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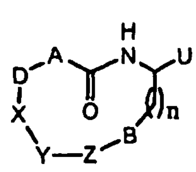
(54) Title: MACROCYCLES USEFUL IN THE TREATMENT OF ALZHEIMER'S DISEASE



(X)

(57) Abstract: The present invention is macrocycles of the formula (X): for treating Alzheimer's disease and other similar diseases. These compounds include inhibitors of the beta-secretase enzyme for the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in a mammal. The compounds of the invention are useful in pharmaceutical compositions and methods of treatment to reduce A beta peptide formation.

MACROCYCLES USEFUL IN THE TREATMENT OF ALZHEIMER'S DISEASE

This application claims priority to U.S. Provisional Application Ser. Nos. 60/297,505 filed June 12, 2001 and 60/333,082 filed November 19, 2001.

Background of the Invention

1. Field of the Invention

The invention relates to substituted cyclic amides and such compounds that are useful for the treatment of Alzheimer's disease. More specifically, the invention relates to such compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

2. Description of the Related Art

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as well as neurofibrillary

tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin. See, for

example, Sindha et al., 1999, *Nature* 402.537-554 (n501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. *In vivo* processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A beta, and present a normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

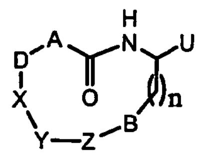
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are effective inhibitors of A beta production, and/or are effective

to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

Summary of the Invention

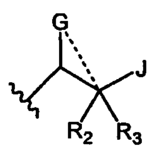
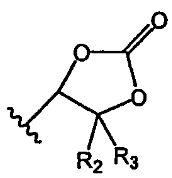
The invention provides compounds of formula (X):



(X)

wherein

U is

 or  ;

--- is an optional bond;

J is $-CH_2OH$ or $-NH-R_c$ when --- is not a bond, or absent when --- is a bond;

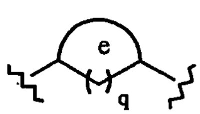
G is OH when --- is not a bond or -O- when --- is a bond;

n is 0-6;

A, B and Y are the same or different and represent

$-(CR_4R_5)_m-$; or

C_2-C_6 alkenyl optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

 , where

q is 0 or 1; and

the "e" ring is

aryl or heteroaryl, each of which is optionally substituted with one, two or three groups

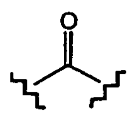
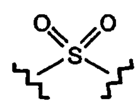
independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

a carbocyclic ring having three, four, five or six atoms in which one, two or three of such atoms are optionally hetero atoms independently selected from O, N, and S and where the carbocyclic ring is optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$;

m is 1-6;

R_4 and R_5 independently are H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, haloC_1-C_6 alkyl, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, or C_3-C_6 cycloalkyl;

D is $-CH_2-$, or

 or ;

X is absent, O, or $-NR_7-$;

Z is absent, O, S, $-NR_7-$, $-C(=O)-$, $-O-C(=O)-$, $-C(=O)-O-$, $-NHC(=O)-$, or $-C(=O)NH-$;

R_7 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl or C_1-C_6 alkoxyalkyl;

R_6, $R_{6'}$ and $R_{6''}$ independently are

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH,

-SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

$-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl), where the alkyl portion is optionally substituted with one, two, three, four, or five groups independently selected from halogen; or

-OH, $-NO_2$, halogen, $-CO_2H$, $-C\equiv N$, $-(CH_2)_{0-4}-CO-NR_8R_9$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-R_{aryl}$, $-(CH_2)_{0-4}-R_{heteroaryl}$, $-(CH_2)_{0-4}-R_{heterocyclyl}$, $-(CH_2)_{0-4}-CO-R_{aryl}$, $-(CH_2)_{0-4}-CO-R_{heteroaryl}$, $-(CH_2)_{0-4}-CO-R_{heterocyclyl}$, $-(CH_2)_{0-4}-CO-R_{10}$, $-(CH_2)_{0-4}-CO-O-R_{11}$, $-(CH_2)_{0-4}-SO_2-NR_8R_9$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-O-R_{11}$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-N(R_{11})_2$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-N(-H$ or $R_{11})-CO-R_8$, $-(CH_2)_{0-4}-NR_8R_9$, $-(CH_2)_{0-4}-R_{10}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{aryl})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{11})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-O-(R_{11})$, $-(CH_2)_{0-4}-O-(R_{11})-COOH$, $-(CH_2)_{0-4}-S-(R_{11})$, C_3-C_7 cycloalkyl, $-(CH_2)_{0-4}-N(-H$ or $R_{11})-SO_2-R_7$, or $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl;

R_8 and R_9 are the same or different and represent -H, $-C_3-C_7$ cycloalkyl, $-(C_1-C_2$ alkyl)$-(C_3-C_7$ cycloalkyl), $-(C_1-C_6$ alkyl)$-O-(C_1-C_3$ alkyl), $-C_1-C_6$ alkenyl, $-C_1-C_6$ alkynyl, or $-C_1-C_6$ alkyl chain with one double bond and one triple bond; or

$-C_1-C_6$ alkyl optionally substituted with -OH or $-NH_2$; or

$-C_1-C_6$ alkyl optionally substituted with one, two or three groups independently selected from halogen; or

heterocyclyl optionally substituted with one, two or three groups selected from halogen, amino, mono- or dialkylamino, -OH, $-C\equiv N$, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, oxo, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen; or

aryl or heteroaryl, each of which is optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6\ \text{alkyl})_2$, $-SO_2-(C_1-C_4\ \text{alkyl})$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, and $-CO-N(C_1-C_6\ \text{alkyl})_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three of halogen;

R_{10} is heterocyclyl optionally substituted with one, two, three or four groups independently selected from C_1-C_6 alkyl;

R_{11} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-R_{aryl}$, or $-(CH_2)_{0-2}-R_{heteroaryl}$;

R_{aryl} is aryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heteroaryl}$ is heteroaryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heterocyclyl}$ is heterocyclyl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, -CO-NH-C_1-C_6 alkyl, =O, -CO-N(C_1-C_6 alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

R_2 is

-H; or-$(CH_2)_{0-4}$-R_{aryl} and -$(CH_2)_{0-4}$-$R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl, C_2-C_6 alkynyl or -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino;

R_3 is -H, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$(CH_2)_{0-4}$-R_{aryl}, or -$(CH_2)_{0-4}$-$R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

$-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a carbocycle of three, four, five, six, or seven carbon atoms, where one atom is optionally a heteroatom selected from the group consisting of -O-, -S-, $-SO_2-$, and $-NR_8-$;

R_C is hydrogen, $-(CR_{245}R_{250})_{0-4}$-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-aryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-aryl, $-[C(R_{255})(R_{260})]_{1-3}-CO-N-(R_{255})_2$, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-CH(heterocyclyl)_2$, -CH(aryl)(heteroaryl), $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH)-(CH_2)_{0-1}$-aryl, $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH-(CH_2)_{0-1}$-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C_1-C_4 alkyl), $-CH(-CH_2-OH)-CH(OH)-phenyl-NO_2$, ($C_1-C_6$ alkyl)-O-(C_1-C_6 alkyl)-OH; $-CH_2-NH-CH_2-CH(-O-CH_2-CH_3)_2$, $-(CH_2)_{0-6}-C(=NR_{235})(NR_{235}R_{240})$, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205}, $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), -SH, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or

$-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205}, $-CO_2H$, and $-CO_2-(C_1-C_4$ alkyl), or

cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocyclyl wherein one, two or three

carbons of the cyclopentyl, cyclohexyl, or cycloheptyl is optionally replaced with a heteroatom independently selected from NH, NR_{215}, O, or $S(=O)_{0-2}$, and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group can be optionally substituted with one or two groups that are independently R_{205}, =O, $-CO-NR_{235}R_{240}$, or $-SO_2-(C_1-C_4$ alkyl), or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R_{200}, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{200} at each occurrence is independently selected from -OH, $-NO_2$, halogen, $-CO_2H$, C≡N, $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-CO-$aryl, $-(CH_2)_{0-4}-CO-$heteroaryl, $-(CH_2)_{0-4}-CO-$heterocyclyl, $-(CH_2)_{0-4}-CO-O-R_{215}$, $-(CH_2)_{0-4}-SO_2-NR_{220}R_{225}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-O-R_{215}$, $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-N-CS-N(R_{215})_2$, $-(CH_2)_{0-4}-N(-H$ or $R_{215})-CO-R_{220}$, $-(CH_2)_{0-4}-NR_{220}R_{225}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(OR_{240})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{215})_2$, $-(CH_2)_{0-4}-O-(R_{215})$, $-(CH_2)_{0-4}-O-(R_{215})-COOH$, $-(CH_2)_{0-4}-S-(R_{215})$, $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with 1, 2, 3, or 5 -F), C_3-C_7 cycloalkyl, $-(CH_2)_{0-4}-N(H$ or $R_{215})-SO_2-R_{220}$, $-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 R_{205} groups, or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1 or 2 R_{205} groups, wherein

the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210};

R_{205} at each occurrence is independently selected from C_1-C_6 alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, NH_2, NH(C_1-C_6 alkyl) or N-(C_1-C_6 alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $-NR_{220}R_{225}$, OH, C≡N, -CO-(C_1-C_4 alkyl), $-SO_2-NR_{235}R_{240}$, $-CO-NR_{235}R_{240}$, $-SO_2$-(C_1-C_4 alkyl), =O, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups;

R_{215} at each occurrence is independently selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}$-(aryl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}$-(heteroaryl), $-(CH_2)_{0-2}$-(heterocyclyl), wherein

the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{210};

R_{220} and R_{225} at each occurrence are independently selected from -H, $-C_3$-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, -C_1-C_6 alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, or

$-C_1$-C_{10} alkyl optionally substituted with -OH, $-NH_2$ or halogen, wherein

the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{270} groups

R_{235} and R_{240} at each occurrence are independently H, or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently selected from -H, C_1-C_4 alkyl, C_1-C_4 alkylaryl, C_1-C_4 alkylheteroaryl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and phenyl; or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO_2-, and -NR_{220}-;

R_{255} and R_{260} at each occurrence are independently selected from -H, -$(CH_2)_{1-2}$-$S(O)_{0-2}$-(C_1-C_6 alkyl), -(C_1-C_4 alkyl)-aryl, -(C_1-C_4 alkyl)-heteroaryl, -(C_1-C_4 alkyl)-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-aryl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-heteroaryl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-heterocyclyl, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{265} at each occurrence is independently -O-, -S- or -N(C_1-C_6 alkyl)-;

R_{270} at each occurrence is independently R_{205}, halogen C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $NR_{235}R_{240}$, -OH, -C≡N, -CO-(C_1-C_4 alkyl), -SO_2-$NR_{235}R_{240}$, -CO-$NR_{235}R_{240}$, -SO_2-(C_1-C_4 alkyl), =O, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or $-(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups;

and pharmaceutically acceptable salts thereof.

The invention also provides intermediates and methods useful for preparing the compounds of formula X.

The invention further provides pharmaceutical compositions comprising a compound of formula X.

The present invention also provides the use of a compound of formula (X) and pharmaceutically acceptable salts thereof for the manufacture of a medicament.

The present invention also provides a method of treating a patient who has Alzheimer's Disease or other diseases that can be treated by inhibiting beta-secretase activity.

Detailed Description of the Invention

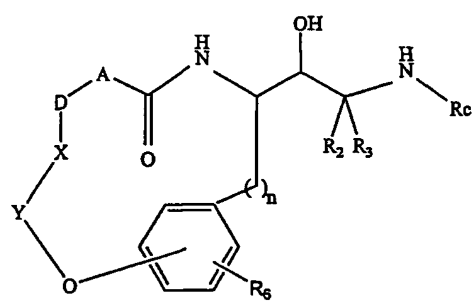
The compounds encompassed by the instant invention are those described by the general formula (X) set forth above, and the pharmaceutically acceptable salts and prodrugs thereof.

In an embodiment, the compounds of formula (X) have syn stereochemistry.

In an embodiment, the compounds of formula (X) have anti stereochemistry.

In an embodiment, the compound of formula (X) includes a pharmaceutically acceptable salt selected from the group consisting of salts of the following acids: hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, TFA, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, HOOC-(CH_2)n-COOH where n is as defined above, HOOC-CH=CH-COOH, and phenyl-COOH.

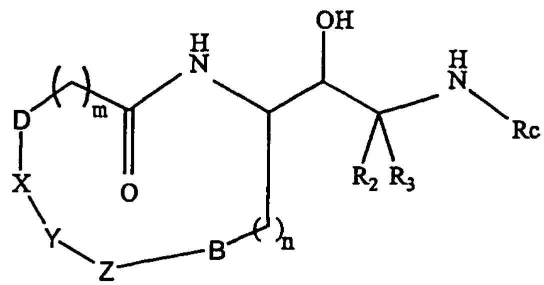
In an embodiment, the compounds of the invention have formula (Xa):



(Xa)

where D, A, X, Y, n, R_2, R_3, R_6 and R_c are as defined above for (X). Preferred compounds of formula (Xa) are those in which the -O- is bonded to the phenyl group at the 3-position relative to the -(alkyl)$_n$ group; Y is C_1-C_6 alkyl; R_6 is halogen; n is 1; R_2 and R_3 are hydrogen; and R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}.

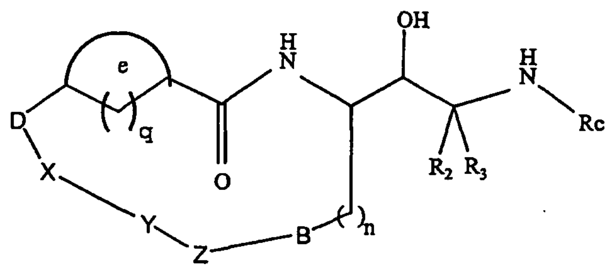
In another embodiment, the compounds of the invention have formula (Xb):



(Xb)

where D, X, Y, Z, B, m, n, R_2, R_3, R_6 and R_c are as defined above for (X). Preferred compounds of formula (Xb) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; and R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}.

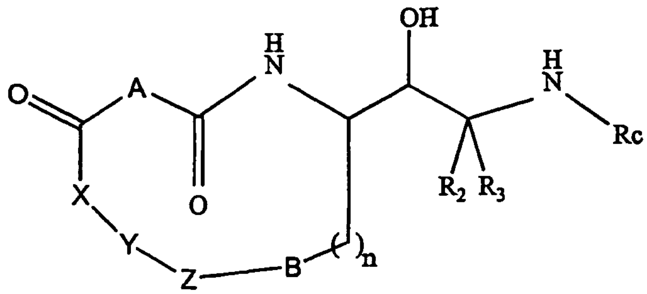
In yet another embodiment, the compounds of the invention have formula (Xc):



(Xc)

where D, X, Y, Z, B, n, the e ring, q, R_2, R_3, and R_c are as defined above for (X). Preferred compounds of formula (Xc) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; and R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}.

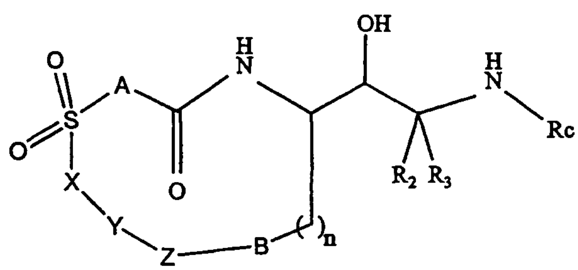
In still another embodiment, the compounds of the invention have formula (Xd):



(Xd)

where A, X, Y, Z, B, n, R_2, R_3, and R_c are as defined above for (X). Preferred compounds of formula (Xd) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}; and X is NR_7.

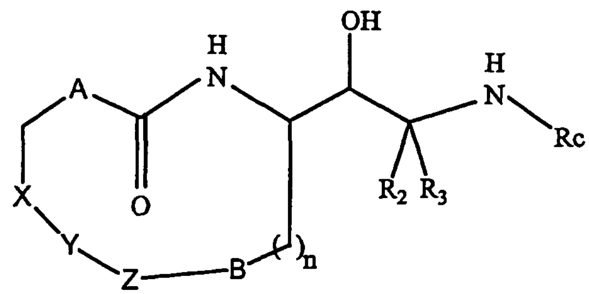
In another embodiment, the compounds of the invention have formula (Xe):



(Xe)

where A, X, Y, Z, B, n, R_2, R_3, and R_c are as defined above for (X). Preferred compounds of formula (Xe) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}; and X is NR_7.

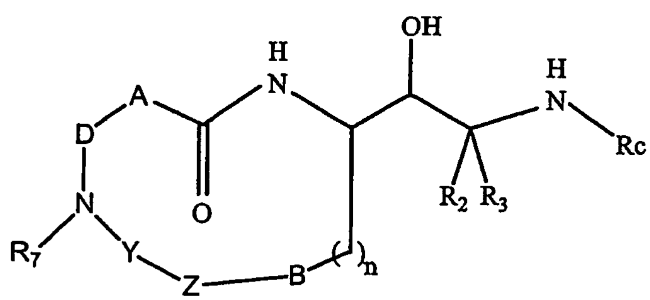
In another embodiment, the compounds of the invention have formula (Xf):



(Xf)

where A, X, Y, Z, B, n, R_2, R_3, and R_c are as defined above for (X). Preferred compounds of formula (Xf) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; and R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}.

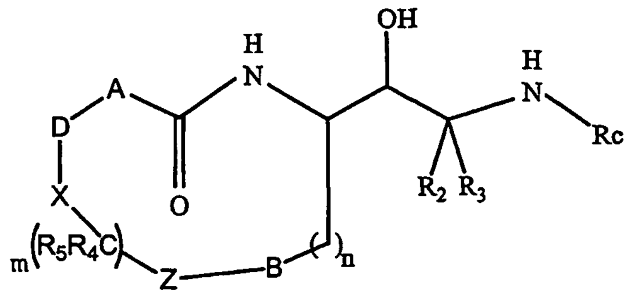
In still another embodiment, the compounds of the invention have formula (Xg):



(Xg)

where A, D, Y, Z, B, n, R_2, R_3, R_7 and R_c are as defined above for (X). Preferred compounds of formula (Xg) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}; and R_7 is hydrogen or C_1-C_6 alkyl.

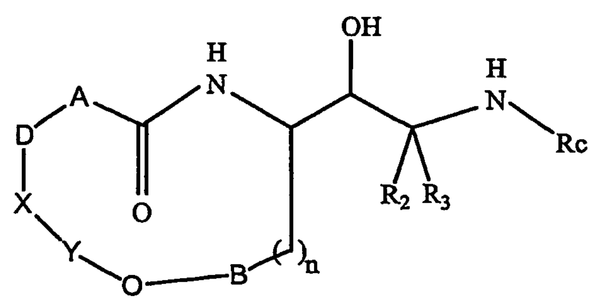
In yet another embodiment, the compounds of the invention have formula (Xh):



(Xh)

where A, D, X, Z, B, m, n, R_2, R_3, R_4, R_5 and R_c are as defined above for (X). Preferred compounds of formula (Xh) are those in which B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}; m is 3-5; and R_4 and R_5 independently are selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloC_1-C_6 alkyl, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, and C_3-C_6 cycloalkyl. More preferred compounds of formula (Xh) are where each R_4 and R_5 is hydrogen, except that one R_4 or R_5 is selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 alkoxyC_1-C_6 alkyl.

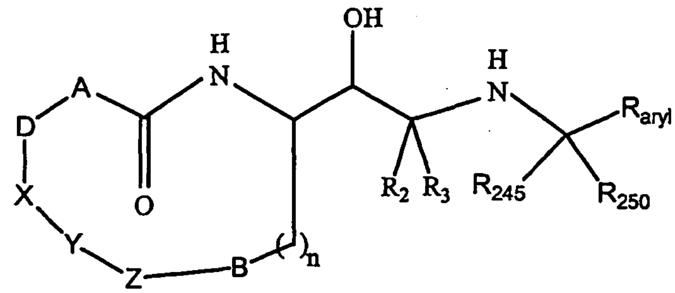
In another embodiment, the compounds of the invention have formula (Xi):



(Xi)

where A, D, X, Y, B, n, R_2, R_3, and R_c are as defined above for (X). Preferred compounds of formula (Xi) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}; X is NR_7; and Y is $-(CR_4R_5)_m$- or C_3-C_6 alkenyl.

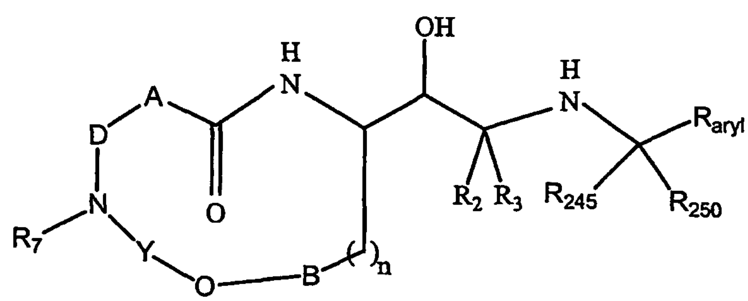
In another embodiment, the compounds of the invention have the formula (Xj):



(Xj)

where A, D, X, Y, Z, B, n, R_2, R_3, R_{245}, R_{250} and R_{aryl} are as defined above for (X). Preferred compounds of formula (Xj) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen or together with the carbon to which they are attached form a three, four, five or six membered carbocycle; R_{aryl} is phenyl optionally substituted with one R_{200}; and R_{245} and R_{250} are hydrogen or together with the carbon to which they are attached form a cyclopropyl.

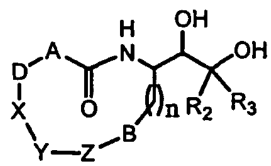
In still another embodiment, the compounds of the invention have the formula (Xk):



(Xk)

where A, D, Y, B, n, R_2, R_3, R_{245}, R_{250} and R_{aryl} are as defined above for (X). Preferred compounds of formula (Xk) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; R_2 and R_3 are hydrogen; R_{aryl} is phenyl optionally substituted with one R_{200}; R_{245} and R_{250} are hydrogen or together with the carbon to which they are attached form a cyclopropyl; and R_7 is hydrogen or lower alkyl.

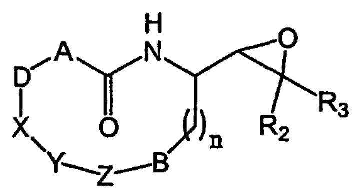
In yet another embodiment, the compounds of the invention have the formula (Xl):



(Xl)

where A, D, Y, B, n, R_2 and R_3 are as defined above for (X). Preferred compounds of formula (Xl) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; and R_2 and R_3 are hydrogen.

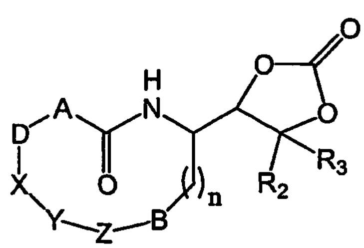
In another embodiment, the compounds of the invention have the formula (Xm):



(Xm)

where A, D, Y, B, n, R_2 and R_3 are as defined above for (X). Preferred compounds of formula (Xm) are those in which Y is C_1-C_6 alkyl; B is aryl optionally substituted with R_6; n is 1; and R_2 and R_3 are hydrogen.

In another embodiment, the compounds of the invention have the formula (Xn):

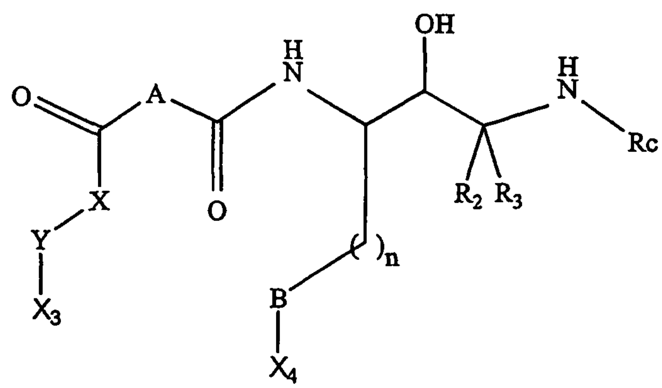


(Xn)

where A, D, Y, B, n, R_2 and R_3 are as defined above for (X). Preferred compounds of formula (Xn) are those in which Y is C_1-C_6

alkyl; B is aryl optionally substituted with R_6; n is 1; and R_2 and R_3 are hydrogen.

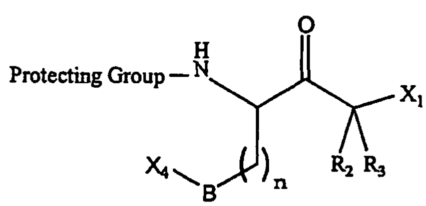
The present invention also includes compounds of the formula (IX):



(IX)

where n, A, X, Y, R_2, R_3, and R_c are as defined above and X_3 and X_4 are comprised of -OH, SH, NHR_7, halogen, pseudohalogen, -$C{=}CH_2$, -C(O)OH or other complimentary functionality that will result in bond formation to give Z; or a chemically acceptable salt thereof.

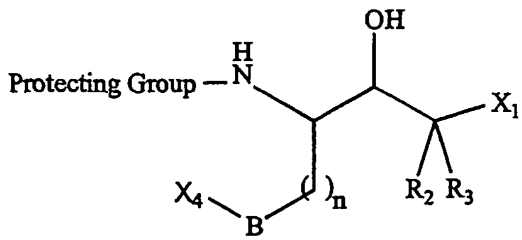
The present invention also includes compounds of the formula (II):



(II)

where n, B, R_2, R_3, and X_4 are as defined above and X_1 is a leaving group including, but not limited to, -Cl, -Br, -I, -O-tosylate, -O-mesylate, -O-nosylate; or a chemically acceptable salt thereof.

The present invention also includes an alcohol of formula (III):



(III)

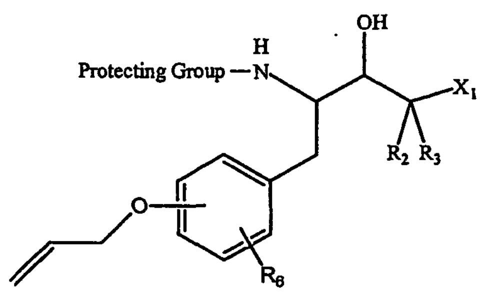
where n, B, R_2, R_3, X_4 and X_1 are as defined above; or a chemically acceptable salt thereof.

In an embodiment, this alcohol includes as Protecting Group t-butoxycarbonyl.

In an embodiment, this alcohol includes as Protecting Group benzyloxycarbonyl.

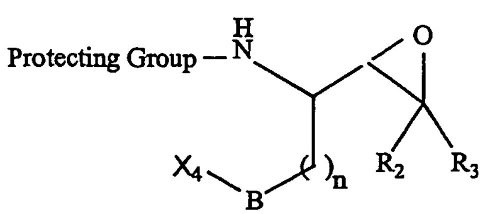
In an embodiment, this alcohol includes as X_1 -Cl or -Br.

In an embodiment, this alcohol has formula (IIIa):



(IIIa)

The present invention also includes an epoxide of the formula (IV):



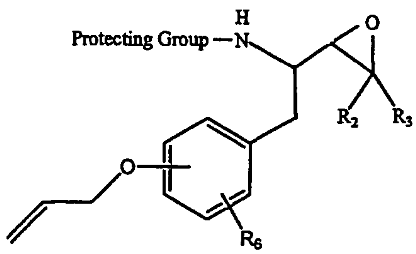
(IV)

where n, B, R_2, R_3, and X_4 are as defined above; or a chemically acceptable salt thereof.

In an embodiment, this epoxide includes as Protecting Group *t*-butoxycarbonyl.

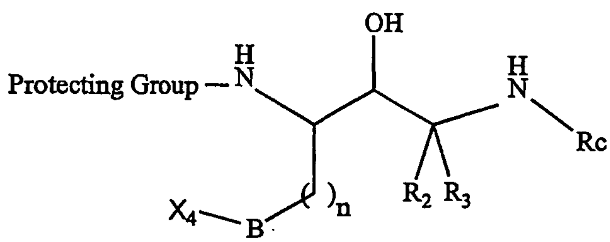
In an embodiment, this epoxide includes as Protecting Group benzyloxycarbonyl.

In an embodiment, this epoxide has formula (IVa):



(IVa)

The present invention also includes a protected alcohol of formula (VI):



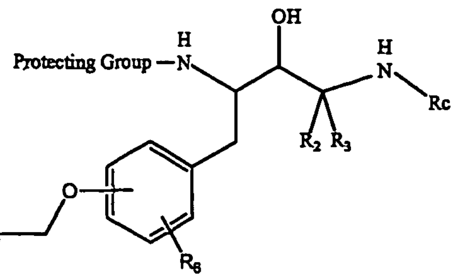
(VI)

where n, B, R_2, R_3, R_c, and X_4 are as defined above; or a chemically acceptable salt thereof.

In an embodiment, this protected alcohol includes as Protecting Group *t*-butoxycarbonyl.

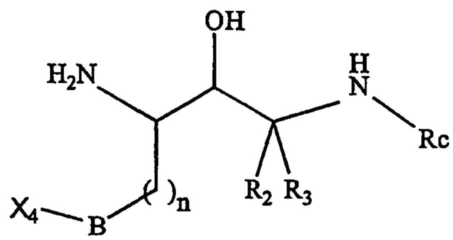
In an embodiment, this protected alcohol includes as Protecting Group benzyloxycarbonyl.

In an embodiment, this protected alcohol has formula (VIa):



(VIa)

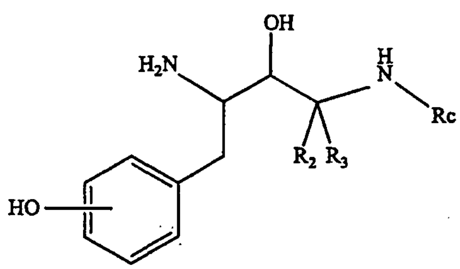
The present invention also includes compounds of the formula (VII):



(VII)

where n, B, R_2, R_3, X_4 and R_c are as defined above; or a chemically acceptable salt thereof.

In an embodiment, this compound of formula (VII) has formula (VIIa):



(VIIa)

The present invention also includes a method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of

Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which includes administration of a therapeutically effective amount of a compound of formula (X) and pharmaceutically acceptable salts thereof.

In an embodiment, this method of treatment can be used where the disease is Alzheimer's disease.

In an embodiment, this method of treatment can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this method of treatment can be used where the disease is mild cognitive impairment.

In an embodiment, this method of treatment can be used where the disease is Down's syndrome.

In an embodiment, this method of treatment can be used where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this method of treatment can be used where the disease is cerebral amyloid angiopathy.

In an embodiment, this method of treatment can be used where the disease is degenerative dementias.

In an embodiment, this method of treatment can be used where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this method of treatment can treat an existing disease.

In an embodiment, this method of treatment can prevent a disease from developing.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 0.5 to about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 1 mg/day to about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily.

In an embodiment, this method of treatment can employ therapeutically effective amounts for oral administration from about 5 mg/day to about 50 mg/day.

The present invention also includes a pharmaceutical composition which includes a compound of the formula (X) and pharmaceutically acceptable salts thereof.

The present invention also includes the use of a compound of formula (X) and pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias,

including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is Alzheimer's disease.

In an embodiment, this use of a compound of formula (X) can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is mild cognitive impairment.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is Down's syndrome.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is cerebral amyloid angiopathy.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is degenerative dementias.

In an embodiment, this use of a compound of formula (X) can be employed where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this use of a compound employs a pharmaceutically acceptable salt selected from the group consisting of salts of the following acids hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, TFA, methanesulfonic, CH_3-$(CH_2)_n$-COOH where n is 0 thru 4, HOOC-(CH_2)n-COOH where n is as defined above, HOOC-CH=CH-COOH, and phenyl-COOH.

The present invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site

between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease characterized by beta-amyloid deposits in the brain which include administration of a therapeutically effective amount of a compound of formula (X) and pharmaceutically acceptable salts thereof.

The present invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of the formula (X) or a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

In an embodiment, this method includes exposing said beta-secretase to said compound *in vitro*.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell in an animal.

In an embodiment, this method includes exposing said beta-secretase to said compound in a human.

The present invention also includes a method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of formula (X) or a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a cleavage site: between Met652 and Asp653, numbered for the APP-751 isotype; between Met 671 and Asp 672, numbered for the APP-770 isotype; between Leu596 and Asp597 of the APP-695 Swedish Mutation; between Leu652 and Asp653 of the APP-751 Swedish Mutation; or between Leu671 and Asp672 of the APP-770 Swedish Mutation.

In an embodiment, this method exposes said reaction mixture *in vitro*.

In an embodiment, this method exposes said reaction mixture in a cell.

In an embodiment, this method exposes said reaction mixture in an animal cell.

In an embodiment, this method exposes said reaction mixture in a human cell.

The present invention also includes a method for inhibiting production of amyloid beta peptide (A beta) in a cell, including administering to said cell an effective inhibitory amount of a compound of formula (X) or a pharmaceutically acceptable salt thereof.

In an embodiment, this method includes administering to an animal.

In an embodiment, this method includes administering to a human.

The present invention also includes a method for inhibiting the production of beta-amyloid plaque in an animal, including administering to said animal an effective inhibitory amount of a

compound of the formula (X) or a pharmaceutically acceptable salt thereof.

In an embodiment, this method includes administering to a human.

The present invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits in the brain including administering to a patient an effective therapeutic amount of a compound of the formula (X) or a pharmaceutically acceptable salt thereof.

Preferably, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

Preferably, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

This method even more preferably employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In a particular preferred embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 0.1 to about 1000 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 15 to about 1500 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 1 to about 100 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 5 to about 50 mg/day.

In an embodiment, this method can be used where said disease is Alzheimer's disease.

In an embodiment, this method can be used where said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type.

The present invention also includes a composition including beta-secretase complexed with a compound of formula (X) or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for producing a beta-secretase complex including exposing beta-secretase to a compound of formula (X) or a pharmaceutically acceptable salt thereof, in a reaction mixture under conditions suitable for the production of said complex.

In an embodiment, this method employs exposing *in vitro*.

In an embodiment, this method employs a reaction mixture that is a cell.

The present invention also includes a component kit including component parts capable of being assembled, in which at least one component part includes a compound of formula Xa enclosed in a container.

In an embodiment, this component kit includes lyophilized compound, and at least one further component part includes a diluent.

The present invention also includes a container kit including a plurality of containers, each container including one or more unit dose of a compound of formula (X) or a pharmaceutically acceptable salt thereof.

In an embodiment, this container kit includes each container adapted for oral delivery and includes a tablet, gel, or capsule.

In an embodiment, this container kit includes each container adapted for parenteral delivery and includes a depot product, syringe, ampoule, or vial.

In an embodiment, this container kit includes each container adapted for topical delivery and includes a patch, medipad, ointment, or cream.

The present invention also includes an agent kit including a compound of formula (X) or a pharmaceutically acceptable salt thereof; and one or more therapeutic agent selected from the group consisting of an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody.

The present invention also includes a composition including a compound of formula (X) or a pharmaceutically acceptable salt thereof; and an inert diluent or edible carrier.

In an embodiment, this composition includes a carrier that is an oil.

The present invention also includes a composition including a compound of formula (X) or a pharmaceutically acceptable salt thereof; and a binder, excipient, disintegrating agent, lubricant, or gildant.

The present invention also includes a composition including a compound of formula (X) or a pharmaceutically acceptable salt thereof; disposed in a cream, ointment, or patch.

The present invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

The compounds, compositions, and methods of the invention are for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be

expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using one or more of the assays described herein or known in the art.

By "Protecting Group" in the present invention is meant any suitable organic protecting group such as disclosed in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991. Preferred protecting groups in the present invention are *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycabonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl,

2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobrornyloxycarbonyl, 1-piperidyloxycarbonyl, 9-fluoroenylmethyl carbonate, $-CH-CH=CH_2$, or phenyl-C(=N-)-H.

By "alkyl" and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C_1-C_{10}" indicates a maximum of 10 carbons.

By "alkoxy" and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" and "C_2-C_6 alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl,

propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

"Alkynyl" and "C_2-C_6 alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl,

indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, -COOH, -C(=O)O(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)N(mono- or di-C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl), -O-C(=O)(C_1-C_6 alkyl), -NH-C(=O)-(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)-C(=O)-(C_1-C_6 alkyl), -NH-SO_2-(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)-SO_2-(C_1-C_6 alkyl), -NH-C(=O)NH_2, -NH-C(=O)N(mono- or di-C_1-C_6 alkyl), -NH(C_1-C_6 alkyl)-C(=O)-NH_2 or -NH(C_1-C_6 alkyl)-C(=O)-N-(mono- or di-C_1-C_6 alkyl).

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the present invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl,

benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide,, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl

S,S-dioxide. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, -COOH, -C(=O)O(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)N(mono- or di-C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl), -O-C(=O)(C_1-C_6 alkyl), -NH-C(=O)-(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)-C(=O)-(C_1-C_6 alkyl), -NH-SO_2-(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)-SO_2-(C_1-C_6 alkyl), -NH-C(=O)NH_2, -NH-C(=O)N(mono- or di-C_1-C_6 alkyl), -NH(C_1-C_6 alkyl)-C(=O)-NH_2 or -NH(C_1-C_6 alkyl)-C(=O)-N-(mono- or di-C_1-C_6 alkyl).

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide.

The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl or =O.

Synthesis

The present invention is the compounds (X) for treating and preventing Alzheimer's disease. The anti-Alzheimer's compounds of formula (X) are made by methods well known to those skilled in the art from starting compounds known to those skilled in the art. The process chemistry is well known to those skilled in the art. The most general process to prepare the compounds of formula (X) of the present invention is set forth in CHART A. The chemistry is straight forward and in summary involves the steps of reacting the protected amino acid (I) with diazomethane followed by work-up as described to add a carbon atom and produce the corresponding protected compound (II). Reduction to the corresponding alcohol (III), followed by formation of the corresponding epoxide (IV), ring opening of the epoxide (IV) with a C-terminal amine, R_C-NH_2 (V) produces the corresponding protected alcohol (VI). The nitrogen protecting group is removed to produce the corresponding amine (VII), which is reacted with an amide forming agent of the formula formula X_3-Y-X-D-A- (CO)-X_2 (VIII) to produce the coupled amines (IX). The coupled amines are then cyclized to produce the anti-Alzheimer compounds (X). One skilled in the art will appreciate that these are all well known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical structure of the biologically active compound end product (X) of the invention would be able to prepare them by known methods from

known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the present invention.

The -NH-CH(R_2)(R_3)-CH (OH)- portion of the compounds of formula (X) can be readily prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1993), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1995) and *Tetrahedron Letters*, 38, 619-620 (1997) all disclose processes to prepare hydroxyethylamine type compounds.

CHART A sets forth a general method used in the present invention to prepare the compounds of formula (X). The compounds of formula (X) are prepared by starting with the corresponding N-protected amino acid (I). It is preferred that the N-protecting group be *t*-butoxycarbonyl (BOC) or benzyloxycarbony (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will understand the preferred methods of introducing a *t*-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1999 for guidance. The X_3 and X_4 functional groups will result in Z upon bond formation. The N-protected amino acids (I) are well known to those skilled in the art or can be readily prepared from known compounds by methods well known to those skilled in the art. The compounds of formula (X) of the present invention have at least two enantiomeric centers which give four enantiomers. The present invention relates to all enantiomers.

The first step of the process is to transform the N-protected amino acid (I) to the cooresponding protected compound (II) by two different methods depending on nature of R_2 and R_3. If it is desired that both R_2 and R_3 are -H, then the protected amino acid (I) is reacted with diazomethane, as is well known to

those skilled in the art, followed by reaction with a compound of the formula $H-X_1$ to produce the protected compound (II). X_1 includes -Cl, -Br, -I, -O-tosylate, -O-mesylate, -O-nosylate; it is preferred that $-X_1$ be -Br or -Cl. Suitable reaction conditions include running the reaction in inert solvents; such as but not limited to ether, tetrahydrofuran and the like. The reactions from the protected amino acid (I) to the protected compound (II) are carried out for a period of time between 10 minutes and 1 day and at temperatures ranging from -78° to 20-25°. It is preferred to conduct the reactions for a period of time between 1-4 hours and at temperatures between -30° to -10°. This process adds one methylene group.

Alternatively, the protected compounds of formula (II) can be prepared by first converting the protected amino acid (I) to a corresponding methyl or ethyl ester, according to methods well established in the art, followed by treatment with a reagent of formula X_1-C $(R_2)(R_3)$-X_1 and a strong metal base. The base serves to affect a halogen-metal exchange, where the $-X_1$ undergoing exchange is a halogen selected from chlorine, bromine or iodine. The nucleophilic addition to the ester derivative gives directly the protected compound (II). Suitable bases include, but are not limited to the alkyllithiums including, for example, *sec*-butyllithium, *n*-butyllithium, and *t*-butyllithium. The reactions are preferably conducted at low temperature, such as -78°. Suitable reaction conditions include running the reaction in inert solvents; such as but not limited to, ether, tetrahydrofuran and the like. Where R_2 and R_3 are both hydrogen, then examples of X_1-C $(R_2)(R_3)$-X_1 include dibromomethane, diiodomethane, chloroiodomethane, bromoiodomethane and bromochloromethane. One skilled in the art knows the preferred conditions required to conduct this reaction. Furthermore, if R_2 and/or R_3 are not -H, then by the addition of -C $(R_2)(R_3)$-X_1 to esters of the protected amino acid (I) to produce the protected

compound (II), an additional chiral center will be incorporated into the product, provided that R_2 and R_3 are not the same.

The protected compound (II) is then reduced by means well known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol affording the corresponding alcohol (III). The means and reaction conditions for reducing the protected compound (II) to the corresponding alcohol (III) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78° to elevated temperature up to the reflux point of the solvent employed. It is preferred to conduct the reduction between -78° and 0°. If borane is used, it may be employed as a complex, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, Wiley-VCH Publishers, 1999. The reduction of the protected compound (II) to the corresponding alcohol (III) produces the second enantiomeric center (third enantiomeric center if R_2 and R_3 are not the same). The reduction of the protected compound (II) produces a mixture of enantiomers at the second center of alcohol (III). This enantiomeric and diastereomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, most preferably by HPLC, employing commercially available chiral columns.

The alcohol (III) is transformed to the corresponding epoxide (IV) by means known to those skilled in the art. A preferred means is by reaction with base, for example, but not

limited to, hydroxide ion generated from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include the use of C_1-C_6 alcohol solvents; ethanol is preferred. A common co-solvent, such as for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from -45° up to the reflux temperature of the alcohol employed; preferred temperature ranges are between -20° and 20-25°. Alternatively, the protected compounds of formula IV can be prepared from aziridine XIV (Chart C) by addition of a Grignard of the formula XV prepared by methods known to those skilled in the art. For Example, *Bull. Korean Chem. Soc.* **1996**, *17*, 219. The resulting protected diol XVI is converted to the epoxide IV using methods known to those skilled in the art. For Example, *Tetrahedron* **1992**, *48*, 10515.

The epoxide (IV) is then reacted with the appropriately substituted C-terminal amine; R_C-NH_2 (V) by means known to those skilled in the art which opens the epoxide to produce the desired corresponding enantiomerically pure protected alcohol (VI). The substituted C-terminal amines, R_C-NH_2 (V) of this invention are commercially available or are known to those skilled in the art and can be readily prepared from known compounds.

Suitable reaction conditions for opening the epoxide (IV) include running the reaction in a wide range of common and inert solvents. C_1-C_6 alcohol solvents are preferred and isopropyl alcohol most preferred. The reactions can be run at temperatures ranging from 20-25° up to the reflux temperature of the alcohol employed. The preferred temperature range for conducting the reaction is between 50° up to the reflux temperature of the alcohol employed. When the substituted C-terminal amine (V) is an aminomethyl group where the substituent on the methyl group is an aryl group, for example NH2-CH_2-$R_{C\text{-aryl}}$, and NH_2-CH_2-$R_{C\text{-aryl}}$ is not commercially available it is preferably

prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substitutent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic Transformations, Wiley-VCH Publishers, 1999, p. 615. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by hydrogen/catalyst to give the C-terminal amine (V) of formula NH_2-CH_2-$R_{C\text{-aryl}}$.

The protected alcohol (VI) is deprotected to the corresponding amine (VII) by means known to those skilled in the art for removal of amine protecting group. Suitable means for removal of the amine protecting group depends on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group, know which reagent is preferable for its removal. For example, it is preferred to remove the preferred protecting group, BOC, by dissolving the protected alcohol (VI) in a trifluoroacetic acid/dichloromethane (1/1) mixture. When complete, the solvents are removed under reduced pressure to give the corresponding amine (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if desired, the amine can be purified further by means well known to those skilled in the art, such as for example, recrystallization. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1999.

The amine (VII) is then reacted with an appropriately substituted amide forming agent X_3-Y-X-D-A- (CO)-X_2 (VIII) to produce coupled amines (IX) by nitrogen-acylation means known to

those skilled in the art. Nitrogen acylation conditions for reaction of the amine (VII) with an amide forming agent (VIII) to produce the corresponding compound (IX) are known to those skilled in the art and can be found in R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972. The nitrogen-acylation of primary amines to produce secondary amides is one of the oldest known reactions. The amide forming agents of the formula X_3-Y-X- (CO)-A- (CO)-X_2 (VIII) are readily prepared according to CHART B from known starting materials by methods known in the literature. X_2 comprises -OH (carboxylic acid) or halide (acyl halide), preferably chlorine, or a suitable group to produce a mixed anhydride.

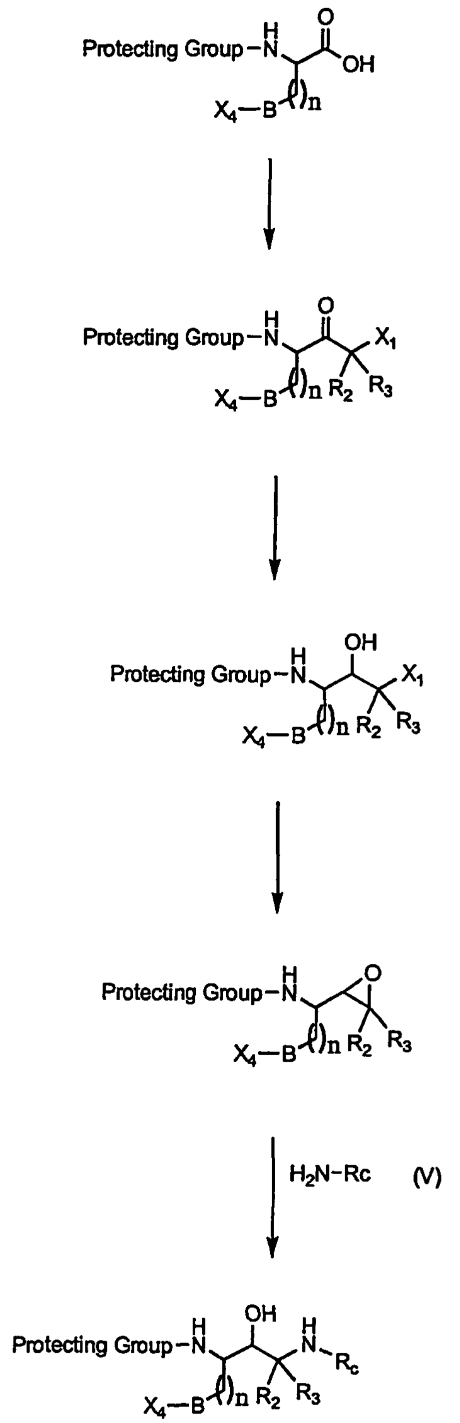
The coupled amine (IX) is cyclized by methods known to those skilled in the art to provide the title compound (X). X_3 comprises -OH, SH, -NHR_7, halogen or pseudohalogen, -C(O)OH to react with X_4 comprising of complimentary functionality that will result in bond formation to give Z. Conditions for effecting the cyclization are amply documented in the literature and readily accessible to those skilled in the art. Further guidance may be found in *Angew. Chem. Int. Ed.* **1999**, *38*, 2345 and references cited therein. *Organic Letters*, **1999**, *1* 953. Conditions for effecting this reaction with macrocyclization are amply documented in the primary literature.

CHART B sets forth a route whereby one may prepare the amide forming agent of the formula X_3-Y-X- (CO)-A- (CO)-X_2 (VIII). The route is exemplified, without the intent of limitation, by the t-butyl ester acid (XI) that can be modified by methods known to those skilled in the art to provide the ester (XII) that upon mild hydrolysis provides the amide forming agent (XIII).

CHART D sets forth an alternative route to compounds (X) for treating and preventing Alzhiemer's disease. The compounds of formula (X) are made by methods well known to those skilled

in the art from starting materials known to those skilled in the art. The process chemistry is well known to those skilled in the art. The chemistry is straight forward and follows many of the generalizations described for CHARTS A-C. In CHART D the coupled amine (XVIII) is transformed to the cyclic carbonate (XIX) by methods known to those skilled in the art. One skilled in the art will understand the preferred methods of introducing and removing cyclic carbonate protecting groups and may additionally consult T.W. Green and P.G.M. Wuts in "*Protective Groups in Organic Synthesis*", John Wiley and Sons, 1999 for guidance. The cyclic carbonate (XIX) is cyclized by methods known to those skilled in the art to provide the diol (XX) after deprotection. X_3 and X_4 are comprised of -OH, SH, NHR_7, halogen, pseudohalogen, $-C{=}CH_2$, -C(O)OH or other complimentary functionality that will result in bond formation to give Z. Conditions for affecting the cyclization are amply documented in the literature and readily accessible to those skilled in the art. Further guidance may be found in *Angew. Chem. Int. Ed.* **1999**, *39*, 2345 and references cited therein and *Organic Letters*, **1999**, *1*, 253. The diol (XX) is transformed to the corresponding epoxide (XXI) by means known to those skilled in the art. A preferred means is by reaction with 1-(*p*-toluenesulfonyl)imidazole followed by potassium t-butoxide. See *Tetrahedron Asymmetry*, **1999**, *10*, 837. Additionally, one can consult *Tetrahedron* **1992**, *48*, 10515 and references therein for further guidance. Opening of the epoxide (XXI) with R_c-NH2 by methods known to those skilled in the art provides the title amine (X).

Chart A



(I)

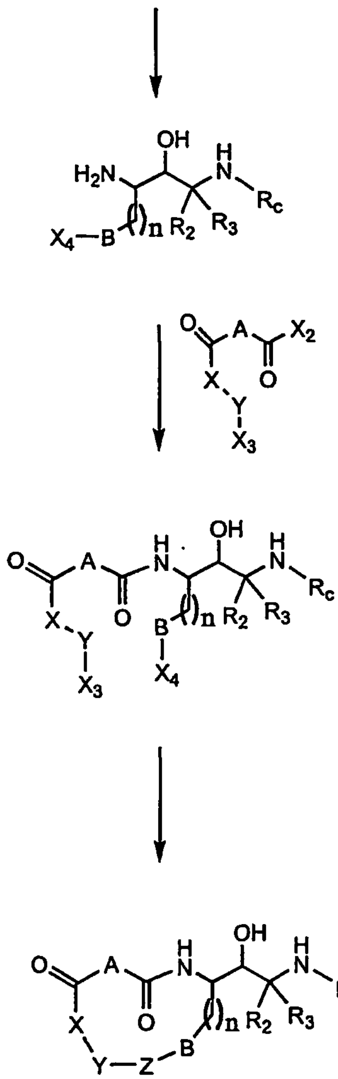
(II)

(III)

(IV)

(VI)

Chart A (cont.)



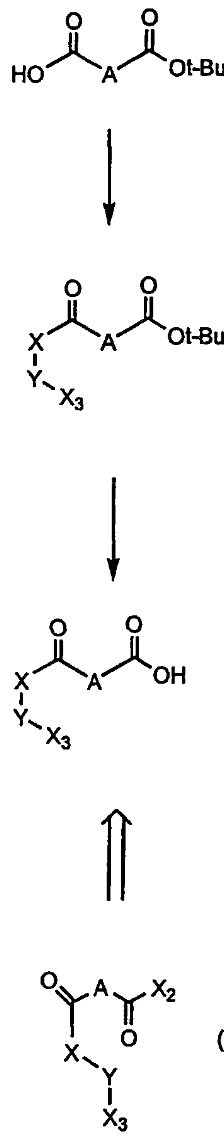
(VII)

(VIII)

(IX)

(X)

Chart B



(XI)

(XII)

(XIII)

(VIII)

Chart C

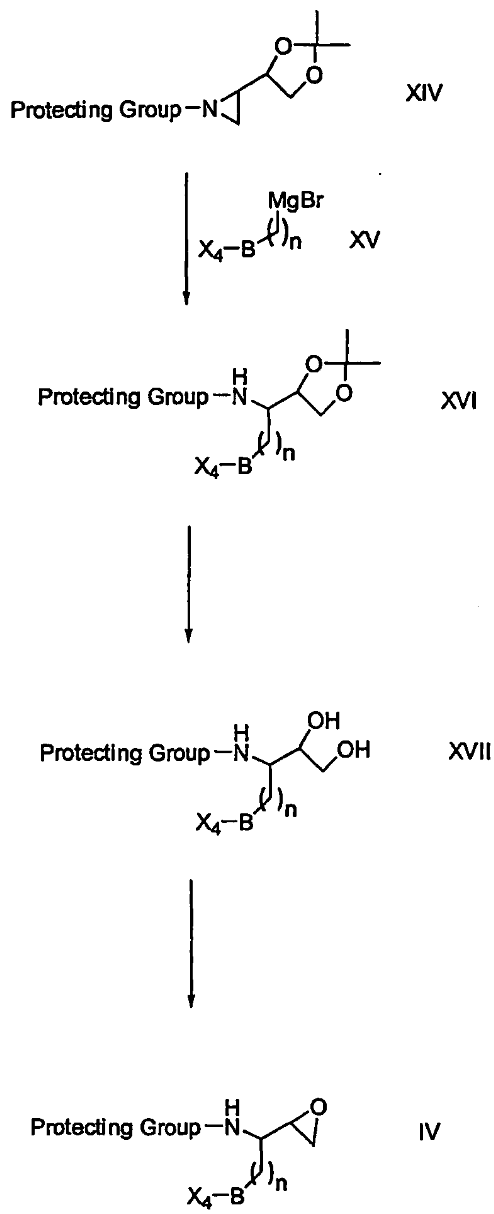


Chart D

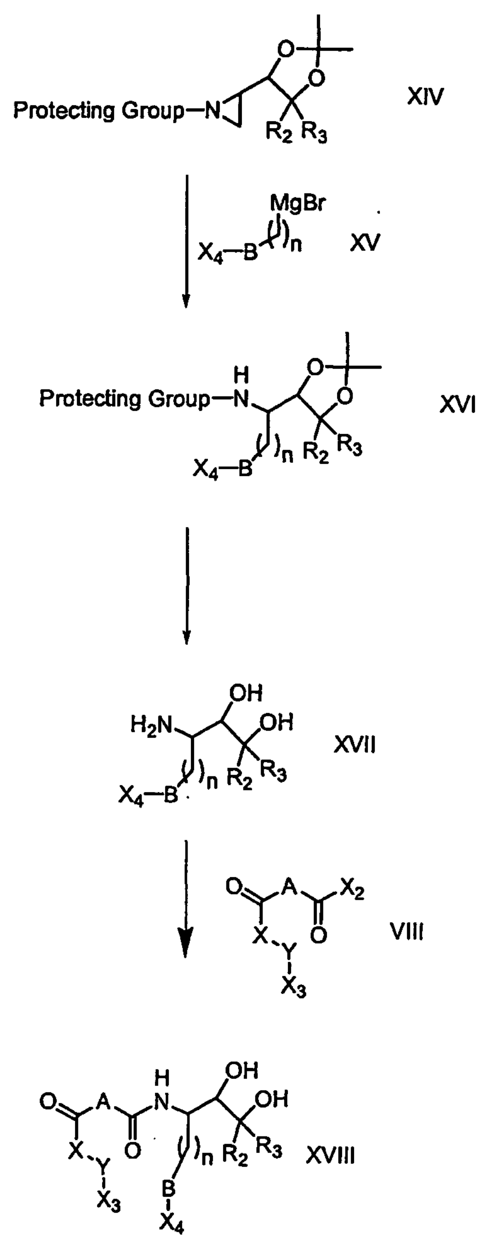
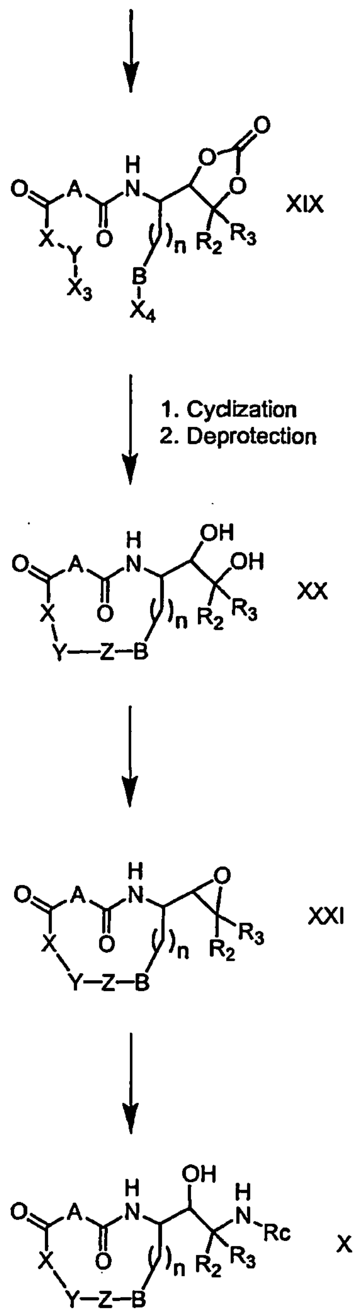

Protecting Group—N
R2 R3
XIV
MgBr
X4—B
n
XV
H
Protecting Group—N
X4—B
n R2 R3
XVI
H2N
OH
OH
X4—B
n R2 R3
XVII
O
A
X2
X
Y
X3
O
VIII
H
N
OH
OH
n R2 R3
B
X4
XVIII

Chart D (Continued)



Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts thereof, are suitable for treating humans and/or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type Alzheimer's disease. In particular, the compounds and compositions of the invention are suitable for treating or preventing Alzheimer's disease. When treating or preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that the compounds of the present invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to

develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the outset of the disease.

Dosage forms and amounts

The compounds of the invention can be administered orally, parenternally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenternal administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage from" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or

the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such

carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampules, vials, and the like for parenternal administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and

duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to,

magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenternal, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenternal preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenternally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in US 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two

weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenternal dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the

therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine

(marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

In addition, the compounds of the present invention can also be used with inhibitors of P-glycoproten (P-gp). The use of P-gp inhibitors is known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of the present invention. To that end the P-gp inhibitor and the compounds of the present invention can be administered at the same time, by the same or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that do the same function.

The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms

are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

There is nothing novel about the route of administration or the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

Inhibition of APP Cleavage

The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the Examples below.

The enzymatic activity of beta-secretase and the production of A beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase

mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

Beta-secretase

Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et.al., 1999, *Mol.Cell.Neurosci.* 14:419-427; Vassar et.al., 1999, *Science* 286:735-741; Yan et.al., 1999, *Nature* 402:533-537; Sinha et.al., 1999, *Nature* 40:537-540; and Lin et.al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than 50 micromolar, preferably at a concentration of 10 micromolar or less, more preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

APP substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet*. 1:233-234, for a review of known variant mutations. Additional substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. Such moieties, include for example, an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett*. 249:21-4, and in U.S. Patent No. 5,612,486. Antibodies used to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that

are specific for human A beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

Assay Systems

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

Cell free assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beat-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification

to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

<u>Cellular assay</u>

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta.

Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP provide a means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A beta.

Although both neural and non-neural cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced processing of APP to A beta, and/or enhanced production of A beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be readily measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

<u>In vivo assays: animal models</u>

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and

5,811,633, and in Ganes et.al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Definitions/Abbreviations

The following abbreviations/definitions are used interchangeably herein:

All temperatures are in degrees Celsius (°C).

TLC refers to thin-layer chromatography.

psi refers to pounds/in^2.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

HOBt refers to 1-hydroxy benzotriazole hydrate.

NMM refers to N-methylmorpholine.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or t-butoxycarbonyl, $-CO-O-C(CH_3)_3$.

CBZ refers to benzyloxycarbonyl, $-CO-O-CH_2$-phenyl.

FMOC refers to 9-fluorenylmethyl carbonate.

TFA refers to trifluoracetic acid, CF_3-COOH.

CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from TMS.

IR refers to infrared spectroscopy.

-phenyl refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit. MH^+ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

TBDMSCl refers to *t*-butyldimethylsilyl chloride.

TBDMSOTf refers to *t*-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in WO00/17369.

"Pharmaceutically acceptable" refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

The present invention provides compounds, compositions, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known synthetic methods.

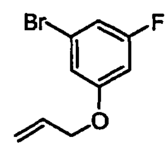
Examples

Synthesis

Example A

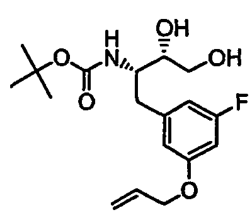
14-[2-(3-ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19), 16(20), 17-triene-8,12-dione (1)

Step One: Preparation of 1-allyloxy-3-bromo-5-fluorobenzene



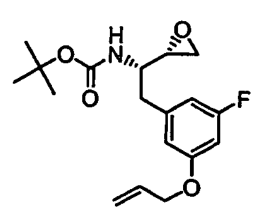
To a DMA (400 ml) solution of allyl alcohol (8.9g, 0.154 mol), at room temperature (r.t.) is added NaH (60% oil dispersion) (6.4 g, 0.160 mol) in portions. The mixture is stirred at r.t. for 1.5 h followed by the slow addition of 3,5-difluoro bromobenzene (17.9 ml, 30 g, 0.155 mol). The reaction mixture is stirred at r.t. overnight. The reaction is quenched by the addition of 1500 ml of water and extracted with ether (4 x 300 ml). The organic layer is dried over $MgSO_4$ and concentrated at reduced pressure to yield 24.6 g (69%) of a colorless oil after flash chromatography (pentane, rf. = 0.3). Anal. Calc. for C_9H_8BrFO: C, 46.78; H, 3.49. Found: C. 46.18, H, 3.45. Calculated mass for C_9H_8OFBr: 229.97. Mass found for C_9H_8OFBr: (OAMS) ES-: 189.0 (M- allyl).

Step Two: Preparation of [1-(3-Allyloxy-5-fluoro-benzyl)-2,3-dihydroxy-propyl]-carbamic acid tert-butyl ester



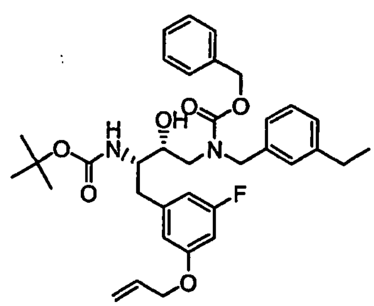
To a flame-dried flask is added Rieke® Mg (5.35 mL, 5.5 mmol) under N_2, with stirring. To this suspension is slowly added 1-allyloxy-3-bromo-5-fluoro-benzene (1.21 g, 5.25 mmol). Once the Grignard reagent is fully formed, it is added via syringe to a THF suspension (1 mL) of CuBr•Me_2S (33.7 mg, 0.163 mmol) at -30°C. After 30 min., a THF (1.0 ml) solution of 2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-aziridine-1-carboxylic acid tert-butyl ester (XIV) (0.50 g, 2.10 mmol) is added via syringe and the reaction mixture slowly warmed to -10°C and stirred for 2 hours. The reaction is quenched with 100 mL NH_4Cl and extracted with EtOAc. The organic layer is washed with $NaHCO_3$, then with brine, and dried with $MgSO_4$, filtered, and concentrated in vacuo, yielding 1.11 g of a yellow oil (100%). The crude product is dissolved in MeOH (50 ml) and treated with Dowex® 50WX2-400 ion-exchange resin (8 eq.) at 50° C. After 2 hours, the mixture is filtered and rinsed alternately with MeOH and DCM (3x). The resin is then treated with 7N NH_3 in MeOH and the filtrate concentrated *in vacuo* to yield crude amino-diol. The amino-diol is dissolved in THF (0.2M) followed by the addition of Boc_2O (0.99 eq.). After work up, flash chromatography (70% EtOAc/Hex) affords the Boc-protected amino-diol as a colorless oil. Calculated mass for $C_{18}H_{26}FNO_5$: 355.18. Mass found for $C_{18}H_{26}FNO_5$: (OAMS) ES+: 256.2 (M- Boc).

<u>Step Three: Preparartion of [2-(3-Allyloxy-5-fluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester</u>



To a CH_2Cl_2 (50 ml) solution of the Boc-protected amino-diol (4.60 g, 12.94 mmol) is added trimethyl orthoacetate (1.69 mL, 13.33 mmol) and *p*-pyridinium toluenesulfonate (32.67 mg, 0.13 mmol). The mixture is stirred at r.t. for 45 minutes, then concentrated *in vacuo* to yield a white solid. The residue is dissolved in CH_2Cl_2 (50 mL), chilled to 0°C, and followed by the addition of TEA (180 µL, 1.29 mmol) and acetyl bromide (0.99 mL, 12.22 mmol). After 45 minutes, the reaction is quenched with $NaHCO_3$, extracted with CH_2Cl_2, and the organic layer is dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue is dissolved in 20% THF/MeOH, followed by the addition of a KOH/MeOH solution (2.25 M) at 0°C. Upon complete reaction, the mixture is diluted with water, extracted into EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield epoxide as a white solid. Calculated mass for $C_{18}H_{24}FNO_4 + H_1$: 338.1767. Accurate mass found for $C_{18}H_{24}FNO_4 + H_1$: 338.1768.

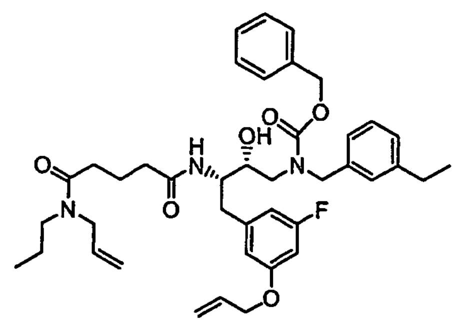
<u>Step Four: Preparation of [4-(3-Allyloxy-5-fluoro-phenyl)-3-tert-butoxycarbonylamino-2-hydroxy-butyl]-(3-ethyl-benzyl)-carbamic acid benzyl ester</u>



To an IPA (50 ml) solution of the epoxide from step three (1.79 g, 5.31 mmol) is added *m*-ethyl benzylamine (3.6 g, 26.55 mmol) with stirring, under N_2. Upon complete reaction, the mixture is concentrated *in vacuo*, redissolved in EtOAc, and

washed with 1N HCl, neutralized with $NaHCO_3$, and dried over Na_2SO_4. The organic layer is filtered, then concentrated *in vacuo*, yielding a white solid (2.55 g). The amine residue is dissolved in THF (25.0 mL), followed by the addition of TEA (0.90 mL, 6.43 mmol) and benzyl chloroformate (0.80 mL, 5.63 mmol) at 0° C. Upon completion the reaction is diluted with EtOAc, washed w/ 1N HCl, washed with $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*, yielding a white solid (3.05 g, 93% yield). Calculated mass for $C_{35}H_{43}FN_2O_6$ + H_1: 607.3183. Accurate mass found for $C_{35}H_{43}FN_2O_6$ + H_1: 607.3195.

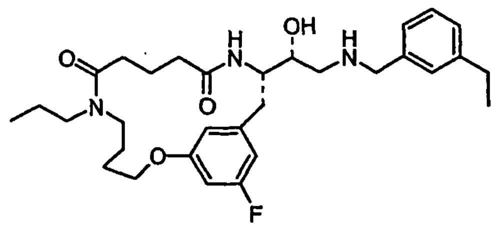
<u>Step Five: Preparation of {4-(3-Allyloxy-5-fluoro-phenyl)-3-[4-(allyl-propyl-carbamoyl)-butyrylamino]-2-hydroxy-butyl}-(3-ethyl-benzyl)-carbamic acid benzyl ester</u>



A solution of [4-(3-Allyloxy-5-fluoro-phenyl)-3-tert-butoxycarbonylamino-2-hydroxy-butyl]-(3-ethyl-benzyl)-carbamic acid benzyl ester (1.84 g, 3.03 mmol) in 20% TFA/DCM (30 mL) is prepared and stirred for 1 hour. The reaction mixture is concentrated *in vacuo* yielding a white solid (2.12 g). Peptide coupling is performed by preparing a solution of 4-(allyl-propyl-carbamoyl)-butyric acid (0.060 g, 2.82 mmol) in CH_2Cl_2 to which is added EDC (0.74 g, 3.84 mmol) and HOBT (0.52 g, 3.84 mmol) under N_2, with stirring. To this solution is added a solution of TEA (1.43 mL, 10.24 mmol), 1-(3-Allyloxy-5-fluoro-

benzyl)-3-[benzyloxycarbonyl-(3-ethyl-benzyl)-amino]-2-hydroxy-propyl-ammonium trifluoro-acetate (1.59 g, 2.56 mmol) dissolved in CH_2Cl_2 (15 mL). Upon complete reaction the mixture is diluted with EtOAc, washed with $NaHCO_3$ and then 1N HCl. The mixture is then neutralized with $NaHCO_3$, and then 0.5N NaOH, treated with activated charcoal, dried with $MgSO_4$, filtered, concentrated *in vacuo*, yielding a yellow oil. Purification is achieved via flash chromatography using 75% EtOAc/Hexanes. Calculated mass for $C_{41}H_{52}FN_3O_6$ + H_1: 702.3918. Accurate mass found for $C_{41}H_{52}FN_3O_6$ + H_1: 702.3916.

Step Six: Preparation of 14-[2-(3-ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19), 16(20), 17-triene-8,12-dione



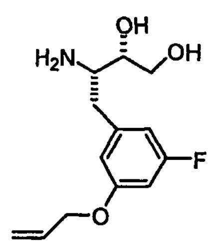
In a glove bag under N_2, is measured tricyclohexylphosphine[1,2-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium(IV)dichloride] (2.38 mg, 0.003 mmol) into a flame-dried flask. To this is added CH_2Cl_2 (50 mL) via syringe and a solution of {4-(3-Allyloxy-5-fluoro-phenyl)-3-[4-(allyl-propyl-carbamoyl)-butyrylamino]-2-hydroxy-butyl}-(3-ethyl-benzyl)-carbamic acid benzyl ester (200 mg, 0.285 mmol) in CH_2Cl_2 (7 mL) via syringe. The reaction mixture is refluxed at 45° C for 1 hour, concentrated *in vacuo*, and purified via radial chromatography with 75% EtOAc/Hexanes, yielding the product as a white solid (136 mg, 70% yield.). 60 mg of the alkene material is dissolved

in MeOH (3 ml) followed by the addition of NH_4OAc (0.003 g, 0.04 mmol) and 10 mg of 10% by wt. Pd/C. The mixture is purged with H_2 and maintained under an atmosphere of H_2 at balloon pressure for 6 hours. The reaction is filtered through Celite and concentrated at reduced pressure to yield a clear oil. The residue is dissolved in MeOH and treated with DOWEX® SBR(-OH) resin for 20 minutes. The resin is removed by filtration and the filtrate concentrated under reduced pressure to yield an off white powder. HRMS calc. for $C_{31}H_{44}FN_3O_4$ + H^+ 542.3394, found 542.3393.

Example B

14-{2-[1-(3-ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione (2)

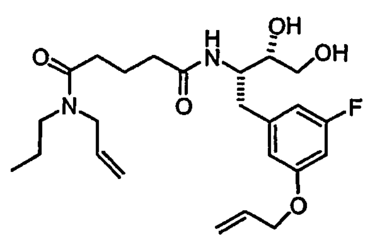
Step One: Preparation of 4-(3-alloxy-5-fluoro-pehny)-3-amino-butane-1,2-diol



To dry 500 ml three neck flask is added Rieke® magnesium (2.5 g, 0.103 mol) as a 115 ml THF suspension. 1-alloxy-3-bromo-5-fluorobenzene (23.2 g, 0.101 mol) is added in 0.5 ml portions to maintain a slight warming of the reaction mixture. Upon complete addition of the bromide, the Grignard solution is transferred via syringe to a THF (15 ml) suspension of $CuBr{\bullet}Me_2S$ (1.6 g, 0.008 mol), at -30°C. The mixture is maintained at -30°C

for 30 min. followed by the addition of Boc-aziridine XIV (9.6 g, 0.040 mol) as a 15 ml solution in THF. The reaction mixture is allowed to warm spontaneously over a 2.5 hour period until LC/MS indicates complete reaction. The reaction mixture is quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers are dried over $MgSO_4$ and concentrated at reduced pressure to yield 9.6 g (61%) of a white solid. The desired amino diol is obtained by dissolving the white solid (3.0 g, 0.008 mol) in MeOH (75 ml) followed by the addition of DOWEX® 50X2-400 ion exchange resin (12.6 g, 0.060 mol) and heating the suspension to 50°C. After 3.5 hours, the mixture is cooled to r.t. and the resin collected by filtration and washed with MeOH and CH_2Cl_2. The resin is then treated with 7N NH_3 in MeOH (3 x 40 ml). The ammonia filtrate is collected and concentrated at reduced pressure to yield 1.9 g of a colorless glass. HRMS calc. for $C_{13}H_{18}FNO_3 + H^+$ 256.1349. Found: 256.1340.

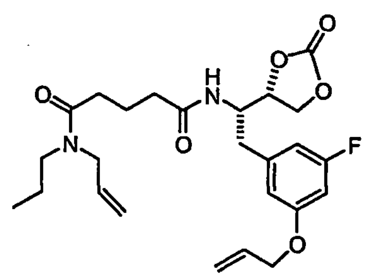
<u>Step Two: Preparation of pentanedioic acid [1-(3-allyloxy-5-fluoro-benzyl)-2,3-dihydroxy-propyl]-amide allyl-propyl-amide</u>



To a DMF (10 ml) solution of 4-(allyl-propyl-carbamoyl)-butyric acid (0.55 g, 2.58 mmol) at r.t. is added EDC (0.58 g, 3.05 mmol) and HOBt (0.41 g, 3.05 mmol). The mixture is stirred at r.t. for 30 minutes followed by the addition of a DMF (10 ml) solution of 4-(3-alloxy-5-fluoro-pehny)-3-amino-butane-1,2-diol (0.60 g, 2.35 mmol) and Et_3N (1.3 ml, 9.4 mmol). The reaction mixture is stirred overnight, then diluted with EtOAc (100 ml)

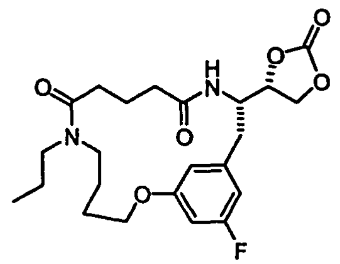
and washed with 1N HCl (2 x 30 ml), 0.5 M NaOH (1 x 30 ml) and brine (1 x 30 ml). The HCl washings are extracted with an additional 20 ml of EtOAc. The combined organic layers are dried over $MgSO_4$ and concentrated at reduced pressure to give 0.85 g (81%) of a slightly yellow oil. HRMS calc. for $C_{24}H_{35}FN_2O_5$ + H^+ 451.2608, found 451.2618.

<u>Step Three: Preparation of pentanedioic acid [2-(3-allyloxy-5-fluoro-phenyl)-1-(2-oxo-[1,3]dioxolan-4-yl)-ethyl]-amide allyl-propyl-amide</u>



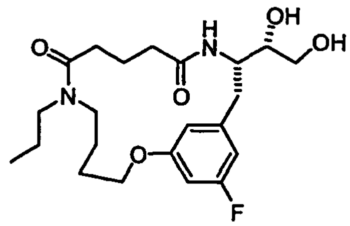
To a THF (15 ml) solution of the diol (0.85 g, 1.9 mmol) and Et_3N (1.32 ml, 9.5 mmol) at r.t. is added a toluene solution of phosgene (1.5 ml, 2.8 mmol). The reaction mixture is stirred at r.t. for 64 hours, then diluted with EtOAc (75 ml), washed with 1N HCl (2 x 25 ml), $NaHCO_3$ (1 x 25 ml) and brine (1 x 25 ml). The organic layer is dried over $MgSO_4$ and concentrate at reduced pressure to yield 0.390 g (43% overall from amino diol) of an amber oil after flash chromatography with EtOAc (rf = 0.24). HRMS calc. for $C_{25}H_{33}FN_2O_6$ + H^+ 477.2401, found 477.2417.

<u>Step Four: Preparation of 18-fluoro-14-(2-oxo-[1,3]dioxolan-4-yl)-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),17-triene-8,12-dione</u>



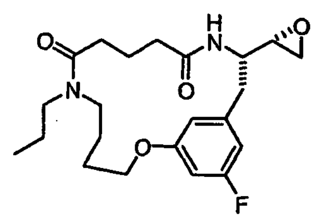
Two separate degassed CH_2Cl_2 (70 ml) solutions of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV) dichloride are each treated with the above di-allyl compound (0.19 g, 0.39 mmol each) of step three in 10 ml of degassed CH_2Cl_2. Each reaction mixture is stirred at r.t. for 2.5 hours at which time LC/MS indicates complete consumption of the starting material. The two reactions are combined and concentrated at reduced pressure to yield 0.260 g of a gray powder after flash chromatography with 5% MeOH/$CHCl_3$ (rf = 0.12). The resulting material is dissolved in MeOH (5 ml) and chilled to 0°C followed by the addition of Pd/C (0.060 g, 10% by wt. carbon). The reaction mixture is purged with H_2 and stirred for 1.5 hours at which time LC/MS indicates complete reaction. The reaction mixture is filtered through Celite and concentrated at reduced pressure to yield 0.230 g (63%) of an off-white foam after radial chromatography 5% MeOH/$CHCl_3$ (rf = 0.15). HRMS calc. for $C_{23}H_{31}FN_2O_6 + H^+$ 451.2244, found 451.2240.

<u>Step Five: Preparation of 14-(1,2-dihydroxy-ethyl)-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione</u>



To a dioxane/MeOH (3:1) solution (4 ml) of the cyclic carbonate, at 0°C is added 1.3 ml of 0.5M NaOH. The mixture is stirred at 0°C for 25 minutes at which time LC/MS shows complete consumption of starting material. The mixture is diluted with EtOAc (70 ml) and washed with NH_4Cl (1 x 20 ml), $NaHCO_3$ (1 x 20 ml) and brine (1 x 20 ml). The organic layer is dried over $MgSO_4$ and concentrated at reduced pressure to yield a white solid. HRMS calc. for $C_{22}H_{33}FN_2O_5 + H^+$ 425.2451, found 425.2433.

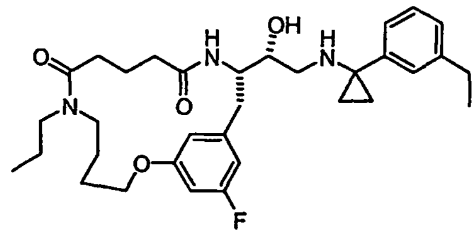
<u>Step Six: Preparation of 18-fluoro-14-oxiranyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione</u>



To a THF/DMF (1:1) solution (1 ml) of the diol (0.060 g, 0.14 mmol) at 0°C is added 1-(*p*-toluenesulfonyl)-imidazole (0.047 g, 0.21 mmol), and the mixture warmed to r.t. over 1 hour. The reaction is then chilled to 0°C followed by the addition of KO*t*-Bu (0.290 ml, 1M in THF). The cold bath is removed and stirring continued at r.t. for 1.5 hours. The reaction is quenched with 20% citric acid (15 ml) and extracted with EtOAc. The organic layer is dried over Na_2SO_4 and

concentrated under reduced pressure to yield a clear glass. Formula wt calc. for $C_{22}H_{31}FNO_4$ 406.49, Ion found (ES+) 407.0. The crude epoxide is combined with another lot and purified to 90% purity (HPLC) by flash chromatography with 2% MeOH/$CHCl_3$. The epoxide is then taken to the next step.

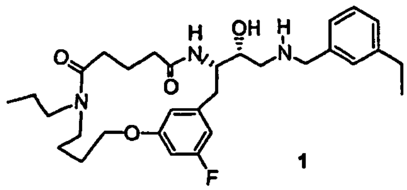
<u>Step Seven: Preparation of 14-{2-[1-(3-ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19), 16(20), 17-triene-8,12-dione</u>



A mixture of the epoxide (0.035 g, 0.086 mmol), 1-(3-ethyl-phenyl)-cyclopropylamine•HCl (0.085 g, 0.4 mmol), and K_2CO_3 (0.083 g, 0.6 mmol) in isopropyl alcohol (1 ml) is heated to 70°C for 15 hours. The reaction mixture is diluted with EtOAc (15 ml) and washed with 1N HCl (2 x 5 ml), $NaHCO_3$ (2 x 5 ml) and brine. The organic layer is dried over Na_2SO_4 and concentrated at reduced pressure to yield 0.015 g (43%) of a clear oil after flash chromatography (10% MeOH/$CHCl_3$; rf = 0.5). Formula weight calc for $C_{33}H_{46}FN_3O_4$ 567.75, Ion found ES+ 568.0.

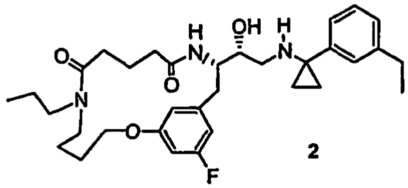
Compounds **1** and **2** above are depicted in Table 1. Also shown below in Table 1 are compounds **3-145**, prepared essentially according to the procedures outlined in CHARTS A-D and set forth in Examples A and B.

Table 1



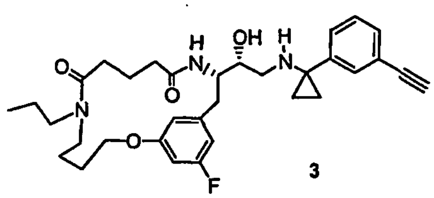
14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

1



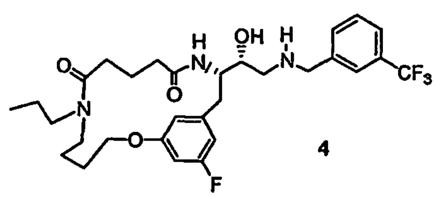
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

2



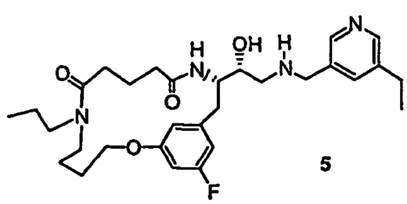
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

3



18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

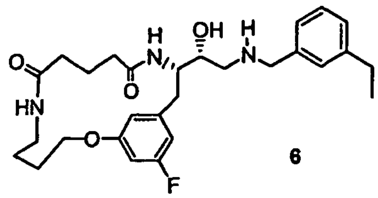
4



14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

5

Table 1 - continued



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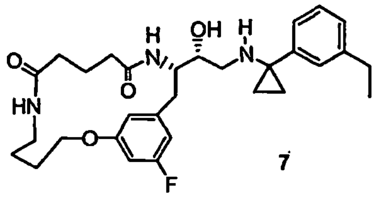
14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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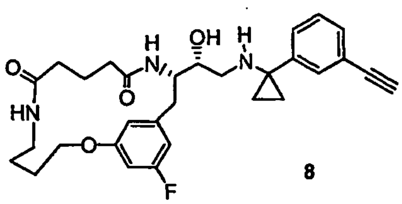
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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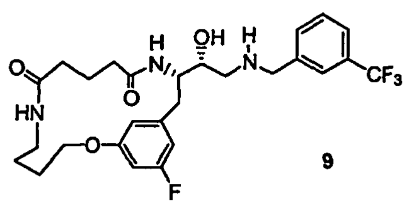
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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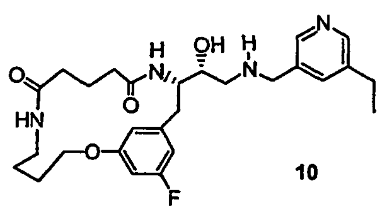
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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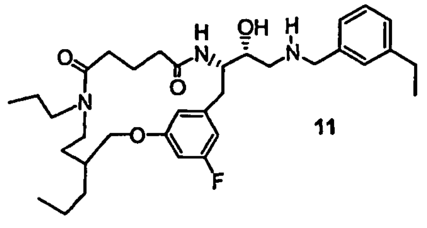
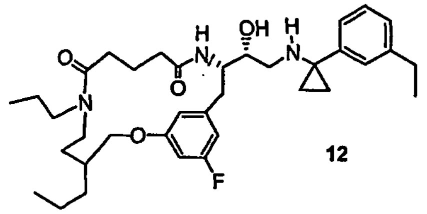
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - continued



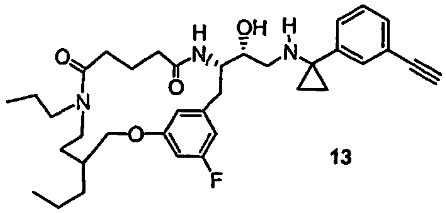
11

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



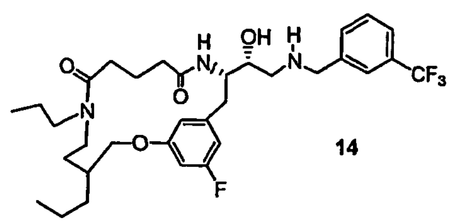
12

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



13

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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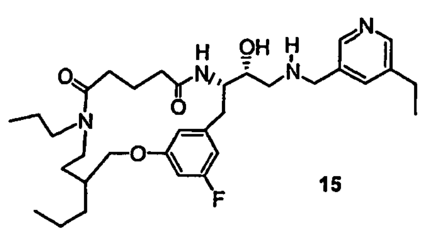
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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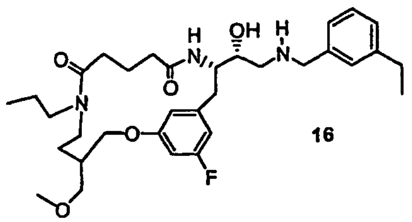
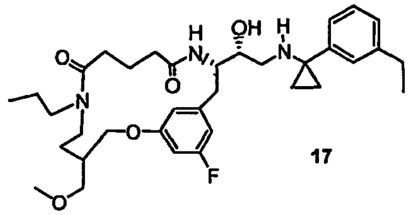
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - Continued



16

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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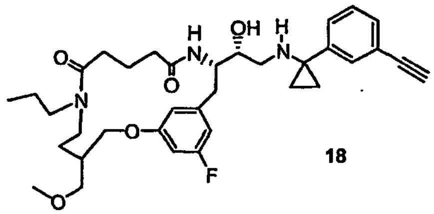
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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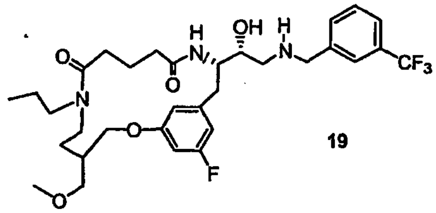
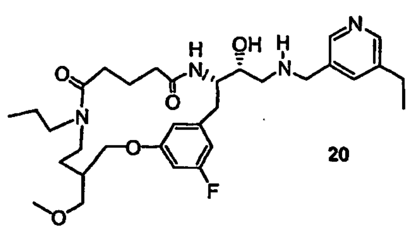
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



19

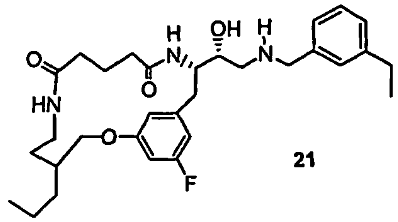
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



20

14-(2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl)-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - Continued



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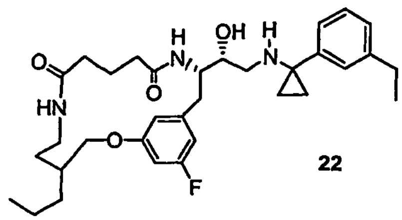

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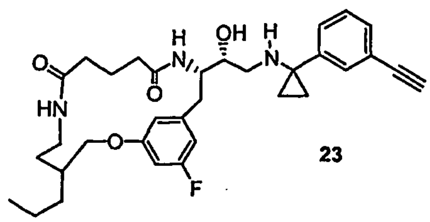

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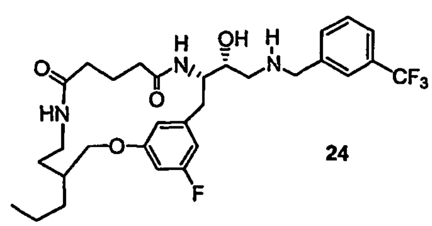

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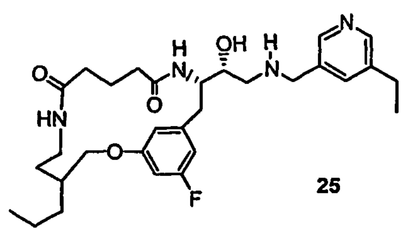

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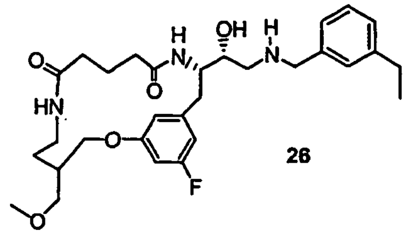
Table 1 - Continued



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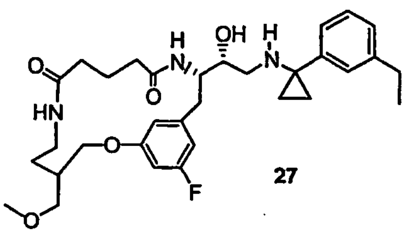

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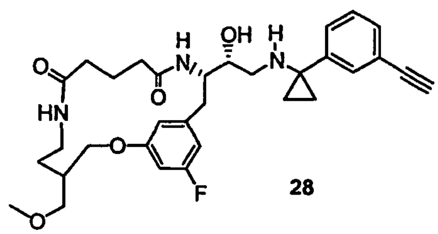

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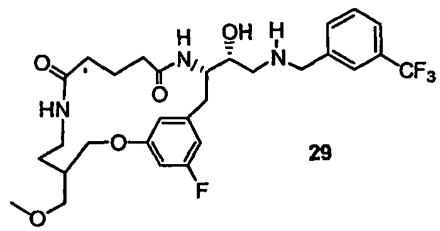

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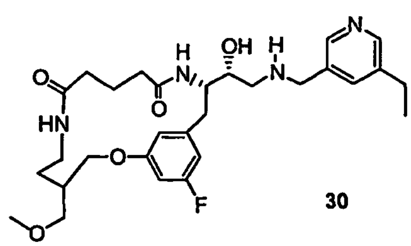

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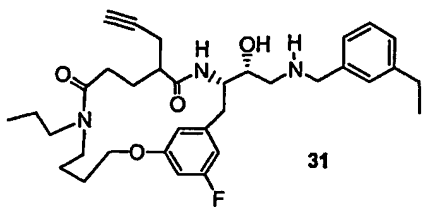
14-(2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl)-18-fluoro-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - Continued



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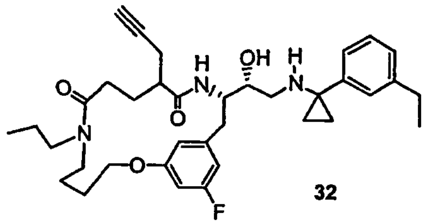
14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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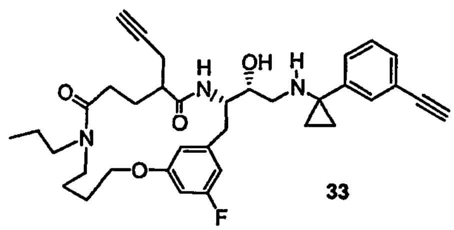

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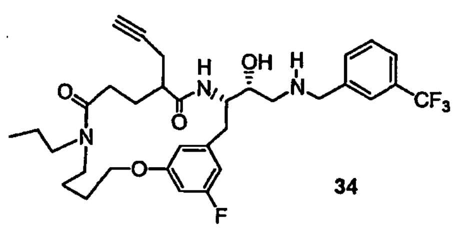

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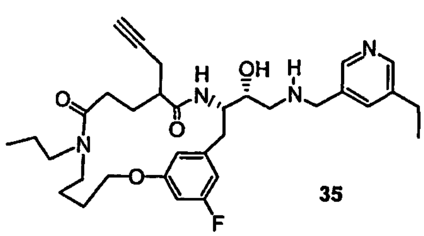
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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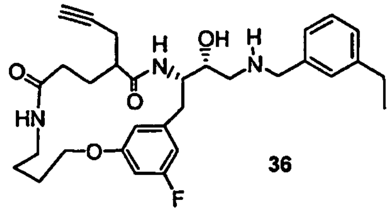
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - Continued



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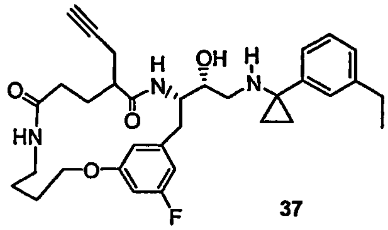

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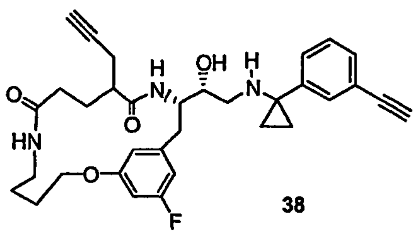

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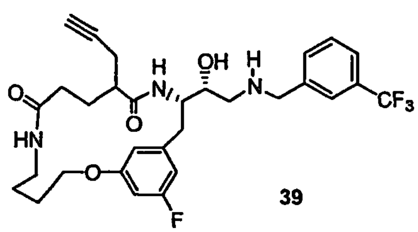

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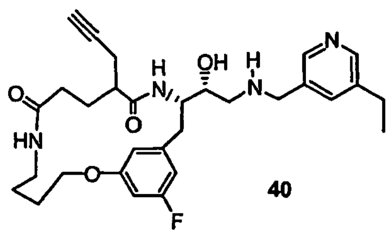
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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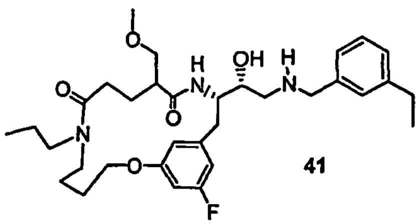
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - Continued



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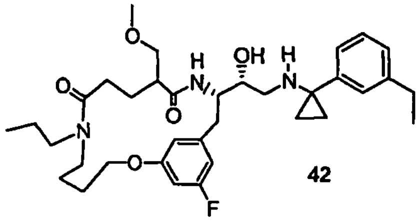

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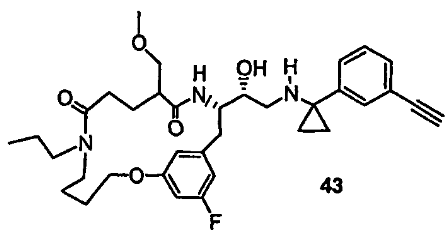
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-h ydroxy-ethyl}-18-fluoro-11-methoxymethyl-7-pro pyl-2-o xa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(2 0),17-triene-8,12-dione



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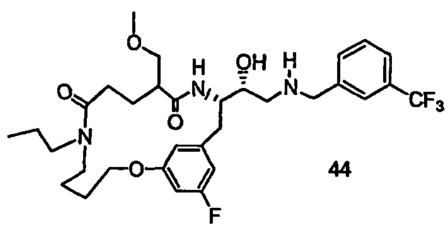

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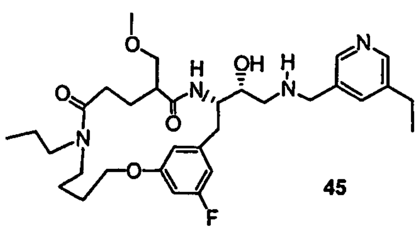
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzyl amino)-ethyl]-11-methoxymethyl-7-propyl-2-oxa-7,1 3-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene -8,12-dione



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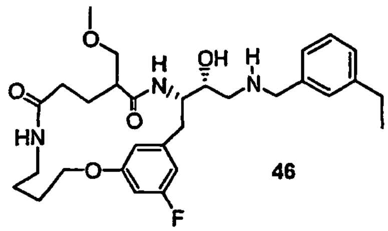
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydro xy-ethyl}-18-fluoro-11-methoxymethyl-7-propyl-2- ox a-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),1 7-triene-8,12-dione

Table 1 - Continued



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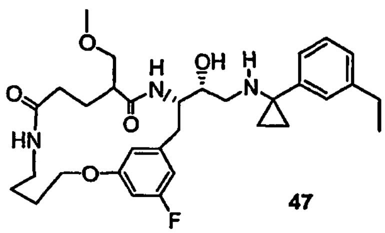
14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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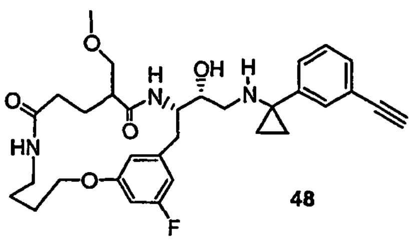
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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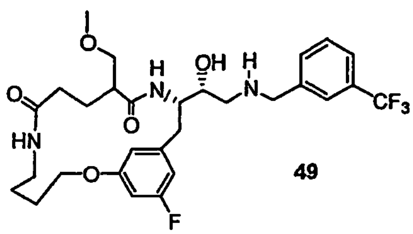
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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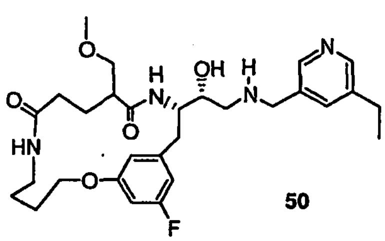
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione



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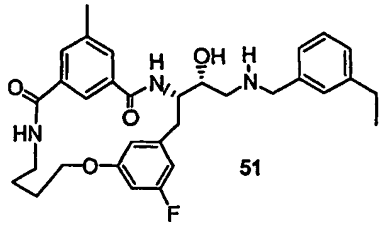
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione

Table 1 - continued



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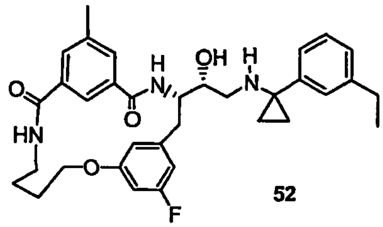
4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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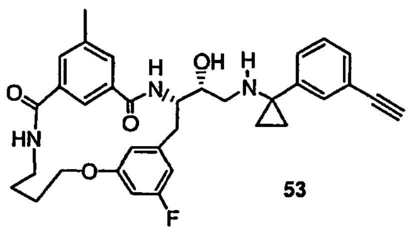
4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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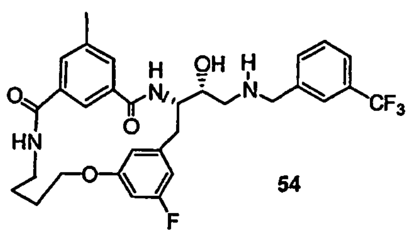
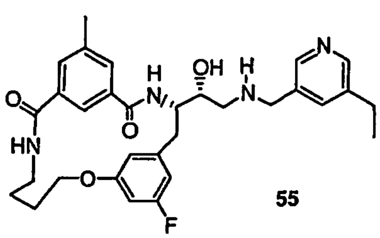
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



54

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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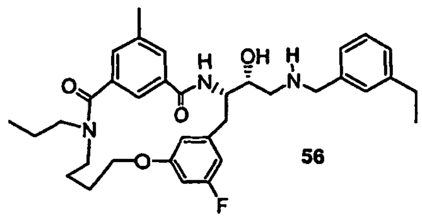
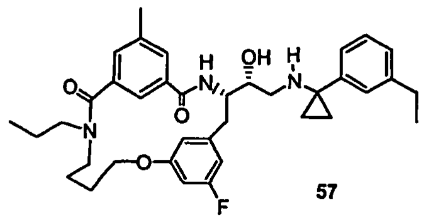
4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione

<u>Table 1 - Continued</u>



56

4-{2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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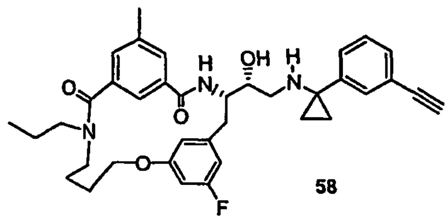
4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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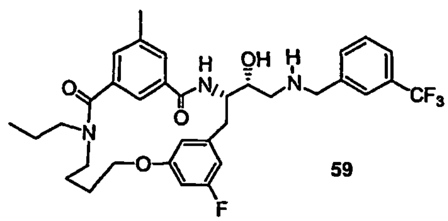
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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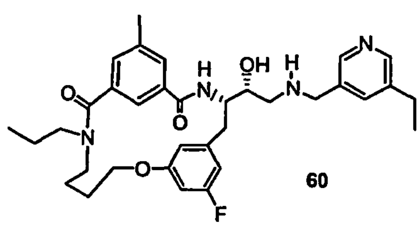
8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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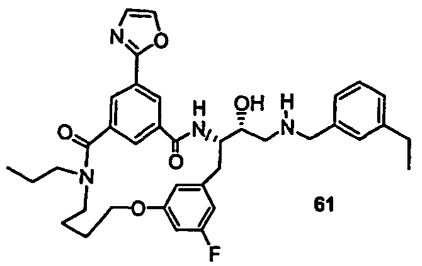
4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione

Table 1 - Continued



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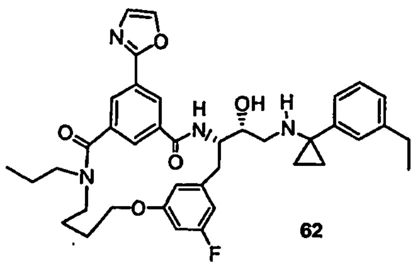
4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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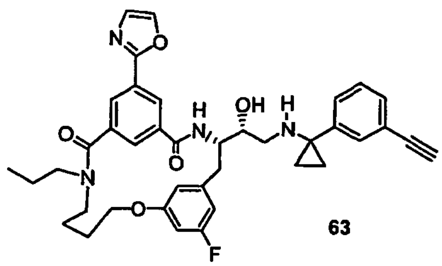
4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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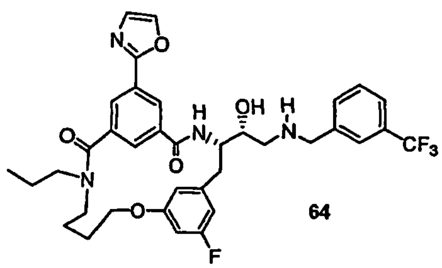
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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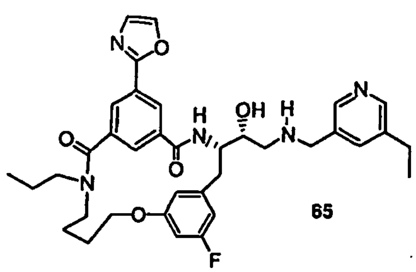
8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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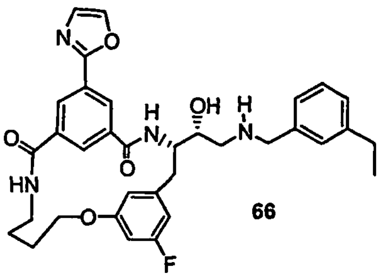
4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione

Table 1 - Continued



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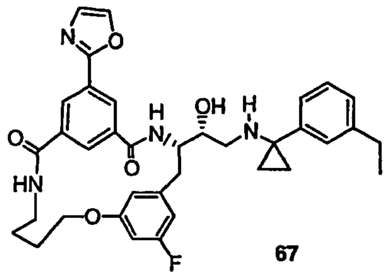
4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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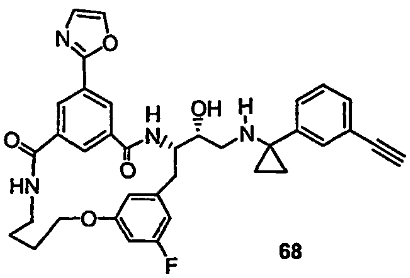
4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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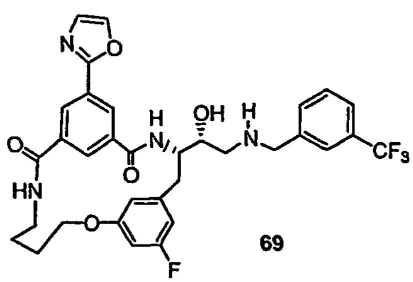
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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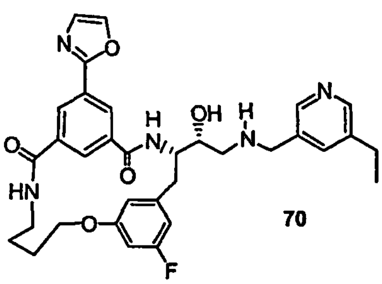
8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione



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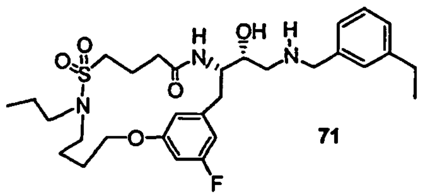
4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione

Table 1 - Continued



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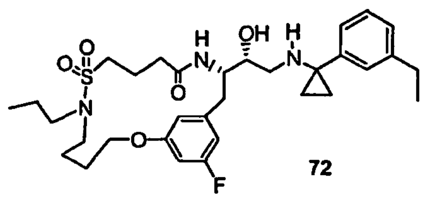
14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ[6]-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one



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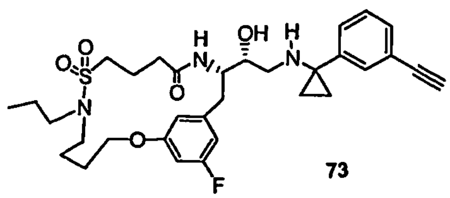
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ[6]-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one



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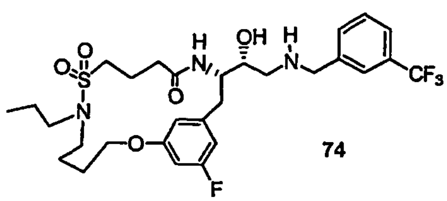
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8f[6]-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one



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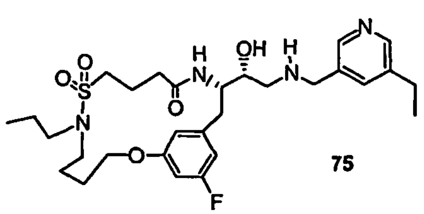
18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-8,8-dioxo-7-propyl-2-oxa-8λ[6]-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one



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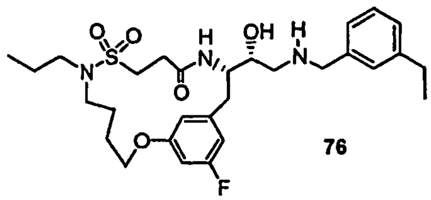
14-(2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl)-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ[6]-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one

Table 1 - Continued



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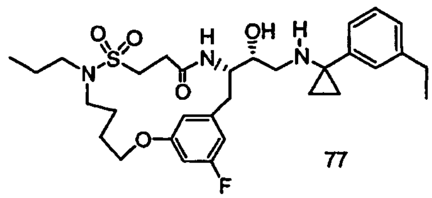
13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one



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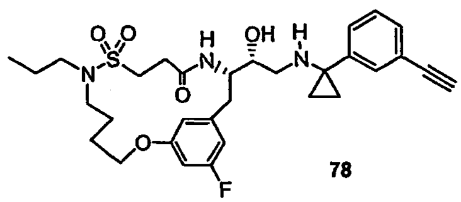
13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one



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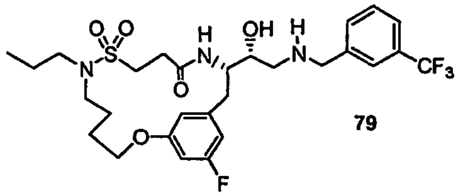

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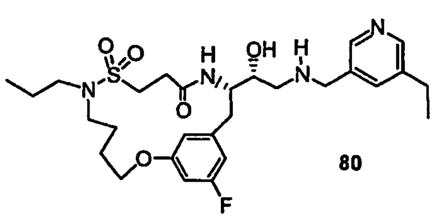
17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one



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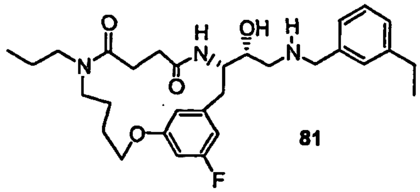
13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one

Table 1 - Continued



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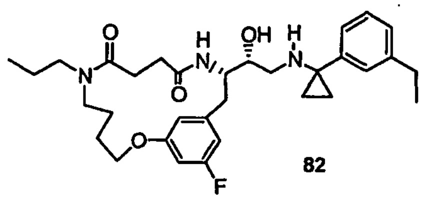
13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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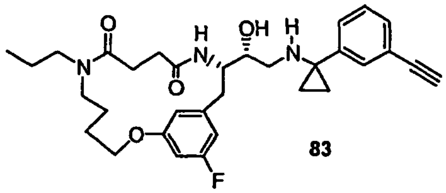
13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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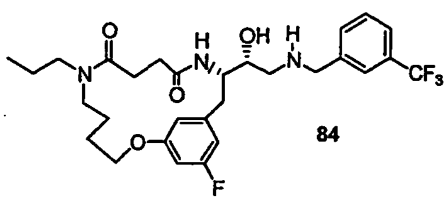

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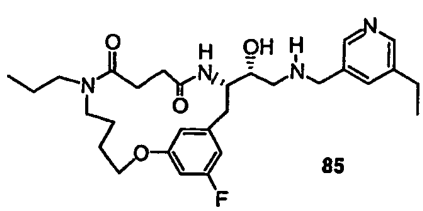
17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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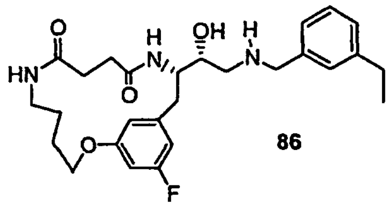
13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione

Table 1 - Continued



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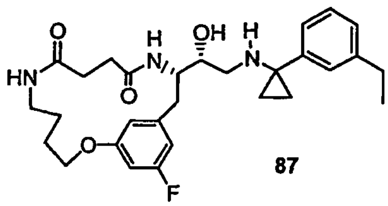
13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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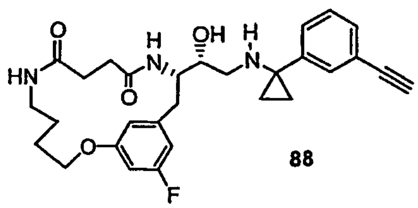

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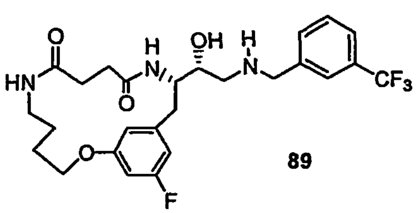

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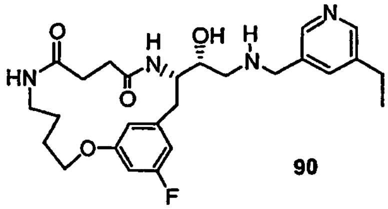
17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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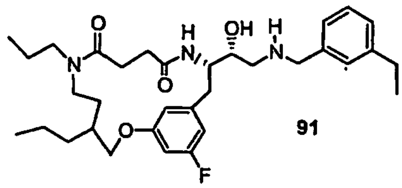
13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione

Table 1 - Continued



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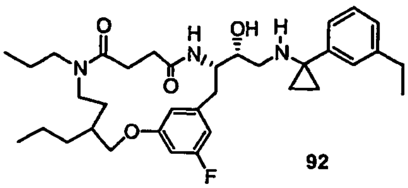

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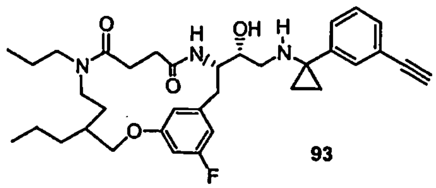

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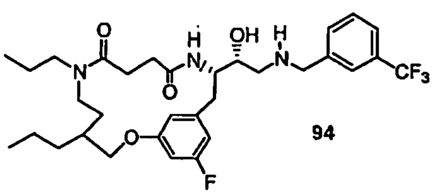
13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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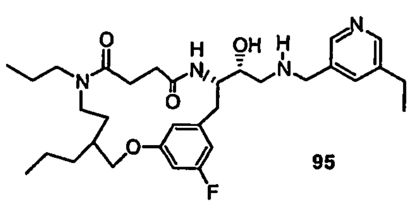

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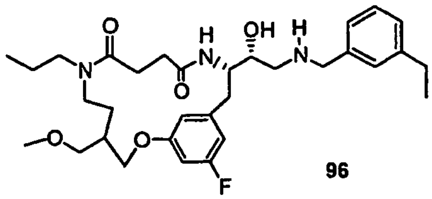
13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione

Table 1 - Continued



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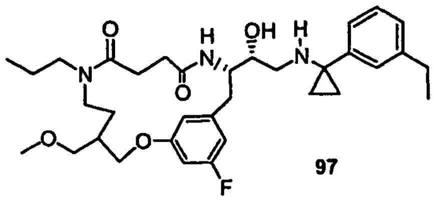

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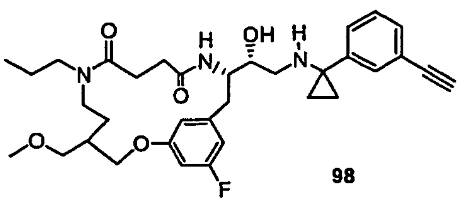

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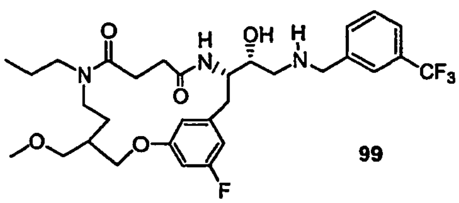

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17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzy lamino)-ethyl]-4-methoxymethyl-7-propyl-2-oxa-7, 12 -diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-tri ene-8,11-dione

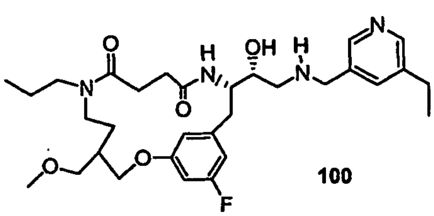

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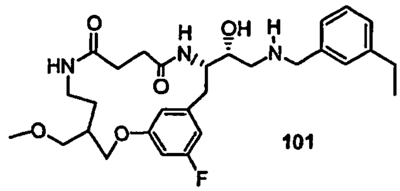
Table 1 - Continued



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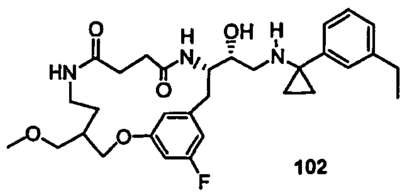

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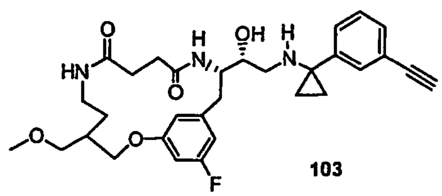

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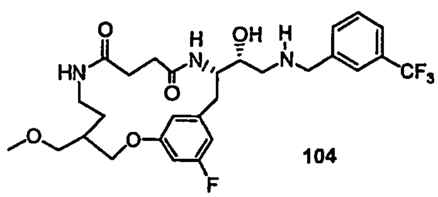
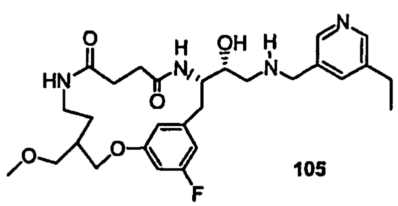
13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



104

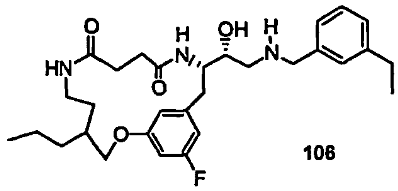
17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



105

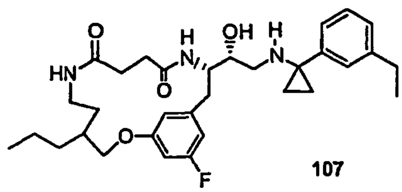
13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione

Table 1 - Continued



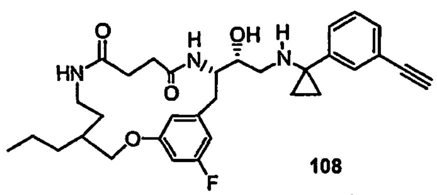
106

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



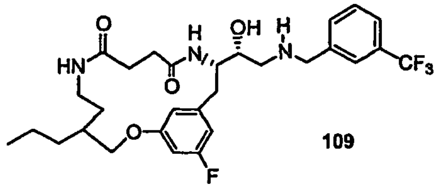
107

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



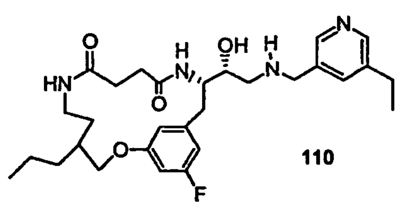
108

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



109

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione



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13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione

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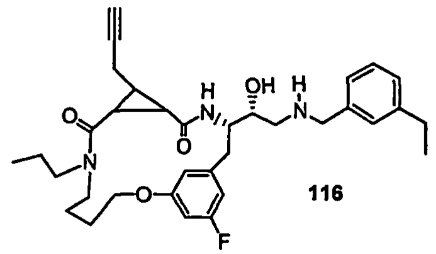
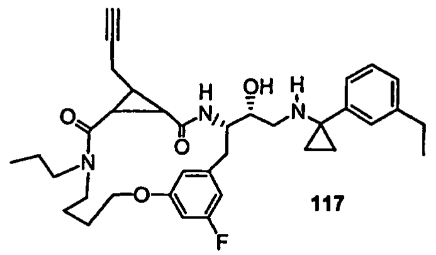


116

3-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione



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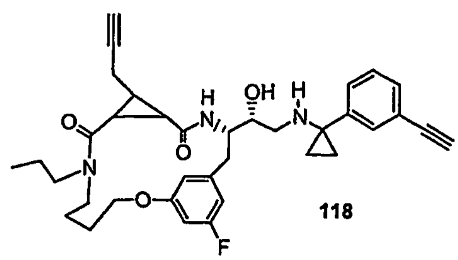
3-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione



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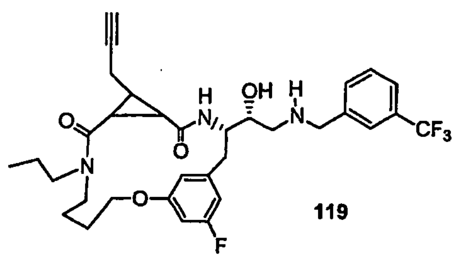

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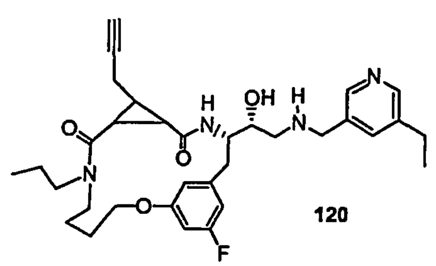
18-Fluoro-3-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione



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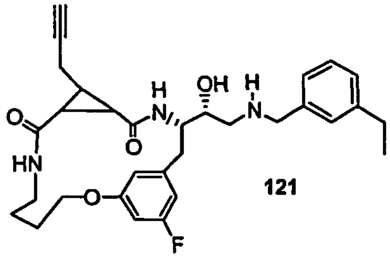
3-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione

Table 1 - Continued



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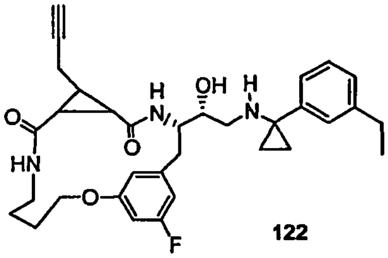
3-{2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.$0^{6,8}$]eicosa-1(20),16,18-triene-5,9-dione



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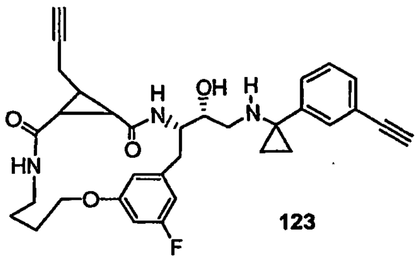
3-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.$0^{6,8}$]eicosa-1(20),16,18-triene-5,9-dione



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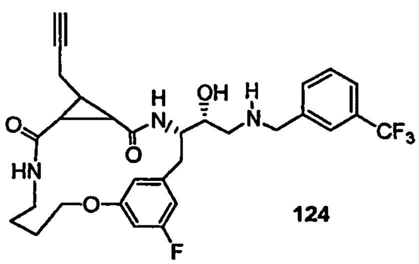
3-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.$0^{6,8}$]eicosa-1(20),16,18-triene-5,9-dione



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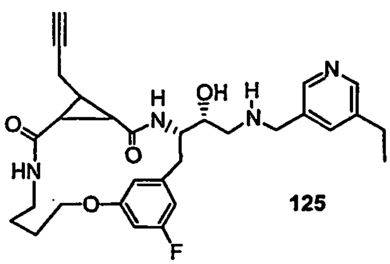
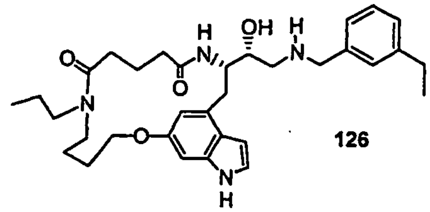
18-Fluoro-3-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.$0^{6,8}$]eicosa-1(20),16,18-triene-5,9-dione



125

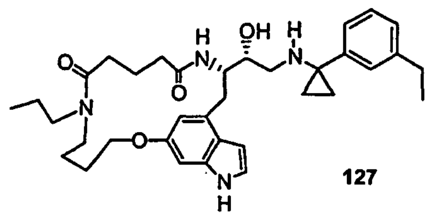
3-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.$0^{6,8}$]eicosa-1(20),16,18-triene-5,9-dione

Table 1 - Continued



126

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione



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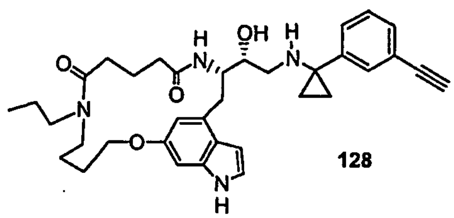
14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione



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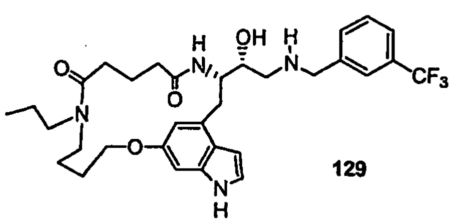
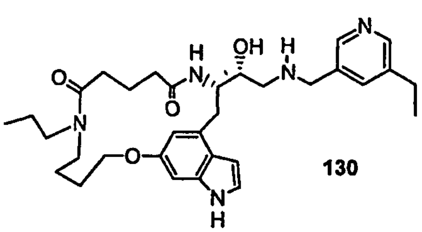
14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione



129

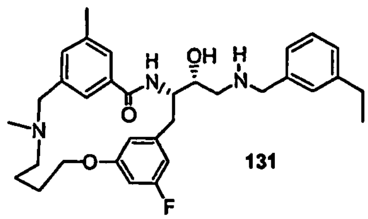
14-[1-Hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione



130

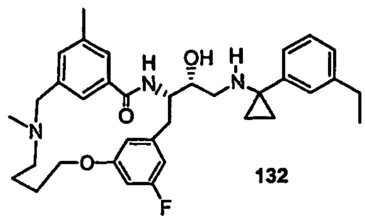
14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione

Table 1 - Continued



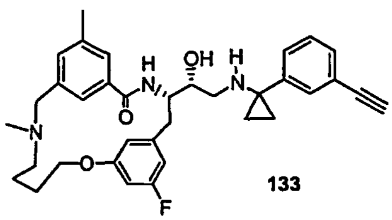
131

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



132

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



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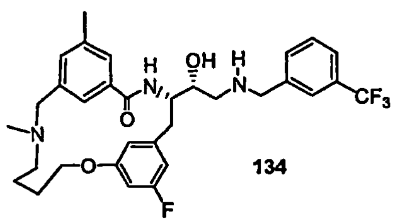
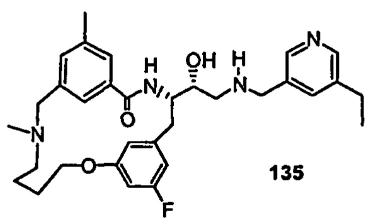
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



134

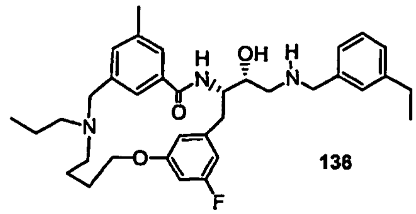
8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



135

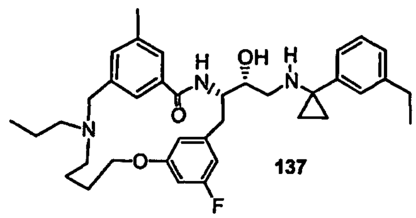
4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one

Table 1 - Continued



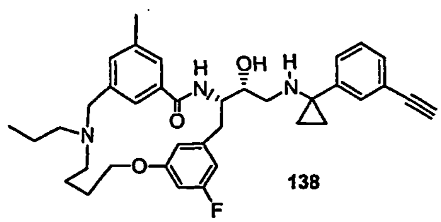
136

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



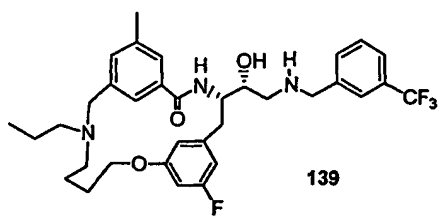
137

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



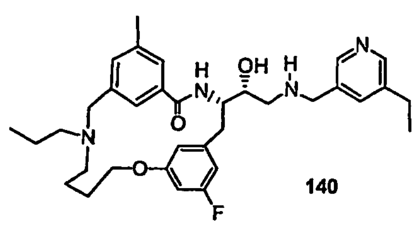
138

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



139

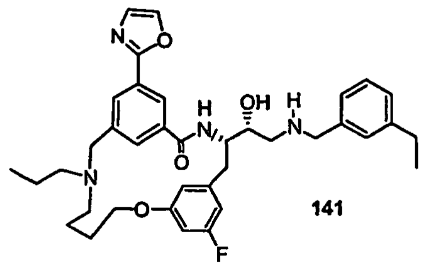
8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



140

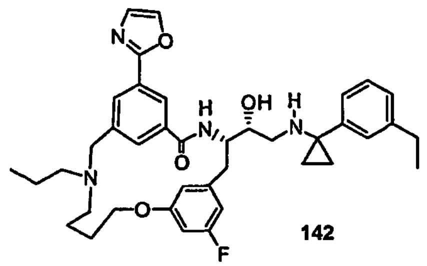
4-(2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one

Table 1 - Continued



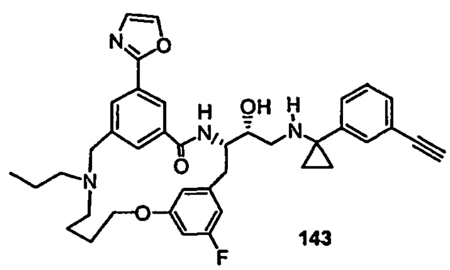
141

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



142

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



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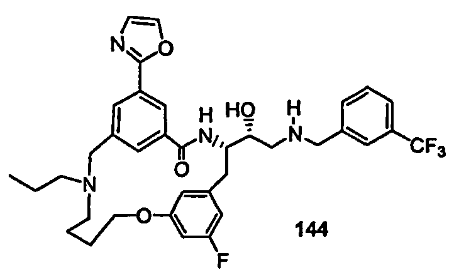
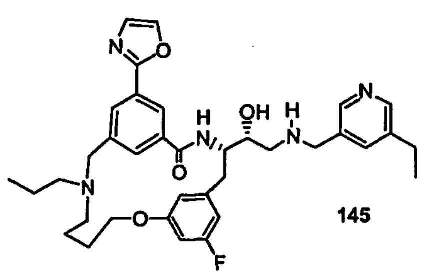
4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



144

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one



145

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one

BIOLOGICAL EXAMPLES

Example A

Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et.al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

Specific Assay Procedure:

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well is transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hours incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added

compound. In this assay, the compounds of the invention exhibited an IC_{50} of less than 50 micromolar.

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Substrates include the following:

Biotin-SEVNL-DAEFRC[oregon green]KK [SEQ ID NO: 1]
Biotin-SEVKM-DAEFRC[oregon green]KK [SEQ ID NO: 2]
Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC[oregon green]KK [SEQ ID NO:4]
Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC[oregon green]KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees C for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acqurest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that

occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, compounds of the invention exhibited an IC50 of less than 50 micromolar.

Example C

Beta-secretase inhibition: P26-P4'SW assay

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence: (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 6]

The P26-P1 standard has the sequence: (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are incubated with strepavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chouromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the

compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

Inhibition of beta-secretase activity - cellular assay

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et.al., 1992, *Nature* 360:672-674), as described in USPN 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

Example F

Inhibition of Beta-Secretase in Animal Models of AD

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et.al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory compounds. As described in USPN 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

Example G

Inhibition of A beta production in human patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the

duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H

Prevention of A beta production in patients at risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

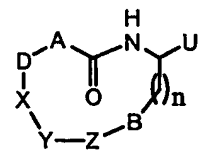
Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood

that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

WHAT IS CLAIMED IS:

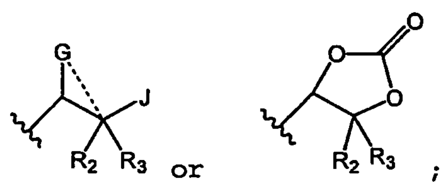
1. A compound of the formula:



(X)

and pharmaceutically acceptable salts thereof wherein

U is



--- is an optional bond;

J is $-CH_2OH$ or $-NH-R_c$ when --- is not a bond, or absent when --- is a bond;

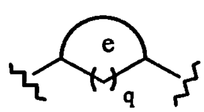
G is OH when --- is not a bond or -O- when --- is a bond;

n is 0-6;

A, B and Y are the same or different and represent

$-(CR_4R_5)_m-$; or

C_2-C_6 alkenyl optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

, where

q is 0 or 1; and

the "e" ring is

aryl or heteroaryl, each of which is optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

a carbocyclic ring having three, four, five or six atoms in which one, two or three of such atoms are optionally hetero atoms independently selected from O, N, and S and where the carbocyclic ring is optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$;

m is 1-6;

R_4 and R_5 independently are H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, haloC_1-C_6 alkyl, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, or C_3-C_6 cycloalkyl;

D is $-CH_2-$, or

X is absent, O, or $-NR_7-$;

Z is absent, O, S, $-NR_7-$, -C(=O)-, -O-C(=O)-, -C(=O)-O-, -NHC(=O)-, or -C(=O)NH-;

R_7 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_1-C_6 alkoxyalkyl;

R_6, $R_{6'}$ and $R_{6''}$ independently are

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

$-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl), where the alkyl portion is optionally substituted with one, two, three, four, or five groups independently selected from halogen; or

-OH, $-NO_2$, halogen, $-CO_2H$, -C≡N, $-(CH_2)_{0-4}-CO-NR_8R_9$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-R_{aryl}$, $-(CH_2)_{0-4}-R_{heteroaryl}$, $-(CH_2)_{0-4}-R_{heterocyclyl}$, $-(CH_2)_{0-4}-CO-R_{aryl}$, $-(CH_2)_{0-4}-CO-R_{heteroaryl}$, $-(CH_2)_{0-4}-CO-R_{heterocyclyl}$, $-(CH_2)_{0-4}-CO-R_{10}$, $-(CH_2)_{0-4}-CO-O-R_{11}$, $-(CH_2)_{0-4}-SO_2-NR_8R_9$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-O-R_{11}$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-N(R_{11})_2$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-N(-H$ or $R_{11})-CO-R_8$, $-(CH_2)_{0-4}-NR_8R_9$, $-(CH_2)_{0-4}-R_{10}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{aryl})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{11})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-O-(R_{11})$, $-(CH_2)_{0-4}-O-(R_{11})-COOH$, $-(CH_2)_{0-4}-S-(R_{11})$, C_3-C_7 cycloalkyl, $-(CH_2)_{0-4}-N(-H$ or $R_{11})-SO_2-R_7$, or $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl;

R_8 and R_9 are the same or different and represent –H, $-C_3-C_7$ cycloalkyl, $-(C_1-C_2$ alkyl)$-(C_3-C_7$ cycloalkyl), $-(C_1-C_6$ alkyl)$-O-(C_1-C_3$ alkyl), $-C_1-C_6$ alkenyl, $-C_1-C_6$ alkynyl, or $-C_1-C_6$ alkyl chain with one double bond and one triple bond; or

$-C_1-C_6$ alkyl optionally substituted with –OH or $-NH_2$; or;

$-C_1-C_6$ alkyl optionally substituted with one, two or three groups independently selected from halogen; or

heterocyclyl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, oxo, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3

alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen; or

aryl or heteroaryl, each of which is optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl$)$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, and $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three of halogen;

R_{10} is heterocyclyl optionally substituted with one, two, three or four groups independently selected from C_1-C_6 alkyl;

R_{11} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-R_{aryl}$, or $-(CH_2)_{0-2}-R_{heteroaryl}$;

R_{aryl} is aryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or

dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heteroaryl}$ is heteroaryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, or $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heterocyclyl}$ is heterocyclyl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$

alkyl, $-SO_2-N(C_1-C_6\ alkyl)_2$, $-SO_2-(C_1-C_4\ alkyl)$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, =O, $-CO-N(C_1-C_6\ alkyl)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

R_2 is

-H; or $-(CH_2)_{0-4}-R_{aryl}$ and $-(CH_2)_{0-4}-R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl, C_2-C_6 alkynyl or $-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino;

R_3 is -H, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_{0-4}-R_{aryl}$, or $-(CH_2)_{0-4}-R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

$-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl optionally substituted with one, two or three groups independently selected from C_1-C_3

alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a carbocycle of three, four, five, six, or seven carbon atoms, where one atom is optionally a heteroatom selected from the group consisting of -O-, -S-, $-SO_2-$, and $-NR_8-$;

R_C is hydrogen, $-(CR_{245}R_{250})_{0-4}$-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-aryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-aryl, $-[C(R_{255})(R_{260})]_{1-3}-CO-N-(R_{255})_2$, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-CH(heterocyclyl)_2$, -CH(aryl)(heteroaryl), $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH)-(CH_2)_{0-1}$-aryl, $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH-(CH_2)_{0-1}$-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C_1-C_4 alkyl), $-CH(-CH_2-OH)-CH(OH)-phenyl-NO_2$, ($C_1-C_6$ alkyl)-O-(C_1-C_6 alkyl)-OH; $-CH_2-NH-CH_2-CH(-O-CH_2-CH_3)_2$, $-(CH_2)_{0-6}-C(=NR_{235})(NR_{235}R_{240})$, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205}, $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), -SH, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or

$-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205}, $-CO_2H$, and $-CO_2-(C_1-C_4$ alkyl), or

cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocyclyl wherein one, two or three carbons of the cyclopentyl, cyclohexyl, or cycloheptyl is optionally replaced with a heteroatom independently

selected from NH, NR_{215}, O, or $S(=O)_{0-2}$, and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group can be optionally substituted with one or two groups that are independently R_{205}, =O, -CO-$NR_{235}R_{240}$, or -SO_2-(C_1-C_4 alkyl), or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R_{200}, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{200} at each occurrence is independently selected from -OH, -NO_2, halogen, -CO_2H, C≡N, -$(CH_2)_{0-4}$-CO-$NR_{220}R_{225}$, -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkynyl), -$(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl), -$(CH_2)_{0-4}$-CO-aryl, -$(CH_2)_{0-4}$-CO-heteroaryl, -$(CH_2)_{0-4}$-CO-heterocyclyl, -$(CH_2)_{0-4}$-CO-O-R_{215}, -$(CH_2)_{0-4}$-SO_2-$NR_{220}R_{225}$, -$(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl), -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl), -$(CH_2)_{0-4}$-N(H or R_{215})-CO-O-R_{215}, -$(CH_2)_{0-4}$-N(H or R_{215})-CO-N$(R_{215})_2$, -$(CH_2)_{0-4}$-N-CS-N$(R_{215})_2$, -$(CH_2)_{0-4}$-N(-H or R_{215})-CO-R_{220}, -$(CH_2)_{0-4}$-$NR_{220}R_{225}$, -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl), -$(CH_2)_{0-4}$-O-P(O)-$(OR_{240})_2$, -$(CH_2)_{0-4}$-O-CO-N$(R_{215})_2$, -$(CH_2)_{0-4}$-O-CS-N$(R_{215})_2$, -$(CH_2)_{0-4}$-O-(R_{215}), -$(CH_2)_{0-4}$-O-(R_{215})-COOH, -$(CH_2)_{0-4}$-S-(R_{215}), -$(CH_2)_{0-4}$-O-(C_1-C_6 alkyl optionally substituted with 1, 2, 3, or 5 -F), C_3-C_7 cycloalkyl, -$(CH_2)_{0-4}$-N(H or R_{215})-SO_2-R_{220}, -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 R_{205} groups, or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1 or 2 R_{205} groups, wherein

the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210};

R_{205} at each occurrence is independently selected from C_1-C_6 alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, NH_2, NH(C_1-C_6 alkyl) or N-(C_1-C_6 alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $-NR_{220}R_{225}$, OH, C≡N, -CO-(C_1-C_4 alkyl), $-SO_2-NR_{235}R_{240}$, $-CO-NR_{235}R_{240}$, $-SO_2$-(C_1-C_4 alkyl), =O, or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups;

R_{215} at each occurrence is independently selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}$-(aryl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}$-(heteroaryl), $-(CH_2)_{0-2}$-(heterocyclyl), wherein

the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{210};

R_{220} and R_{225} at each occurrence are independently selected from -H, $-C_3$-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, -C_1-C_6 alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, or

$-C_1$-C_{10} alkyl optionally substituted with -OH, $-NH_2$ or halogen, wherein

the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{270} groups

R_{235} and R_{240} at each occurrence are independently H, or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently selected from -H, C_1-C_4 alkyl, C_1-C_4 alkylaryl, C_1-C_4 alkylheteroaryl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and phenyl; or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO_2-, and -NR_{220}-;

R_{255} and R_{260} at each occurrence are independently selected from -H, -$(CH_2)_{1-2}$-$S(O)_{0-2}$-(C_1-C_6 alkyl), -(C_1-C_4 alkyl)-aryl, -(C_1-C_4 alkyl)-heteroaryl, -(C_1-C_4 alkyl)-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-aryl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-heteroaryl, -$(CH_2)_{1-4}$-R_{265}-$(CH_2)_{0-4}$-heterocyclyl, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

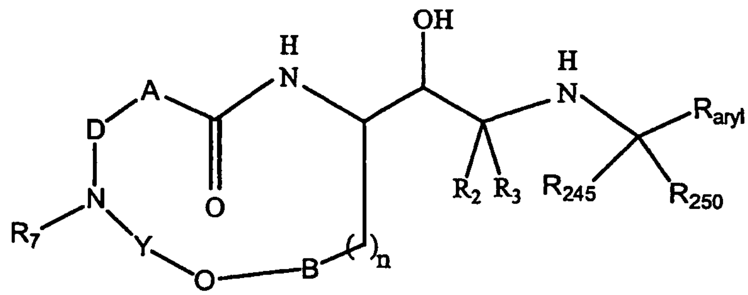
each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{265} at each occurrence is independently -O-, -S- or -N(C_1-C_6 alkyl)-; and

R_{270} at each occurrence is independently R_{205}, halogen C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $NR_{235}R_{240}$, -OH, -C≡N, -CO-(C_1-C_4 alkyl), -SO_2-$NR_{235}R_{240}$, -CO-$NR_{235}R_{240}$, -SO_2-(C_1-C_4 alkyl), =O, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups.

2. A compound according to claim 1 having the formula



3. A compound according to claim 2 wherein

Y is C_1-C_6 alkyl;

B is aryl optionally substituted with R_6;

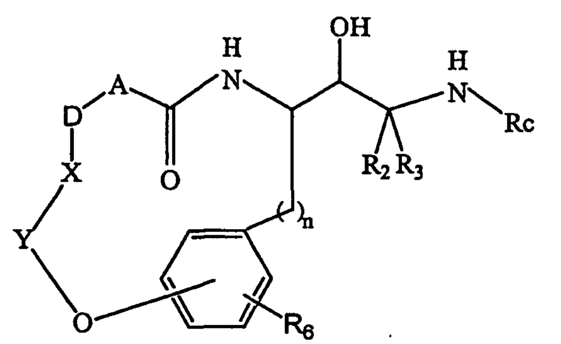
n is 1;

R_2 and R_3 are hydrogen;

R_{245} and R_{250} are hydrogen or together with the carbon atom to which they are attached form cyclopropyl;

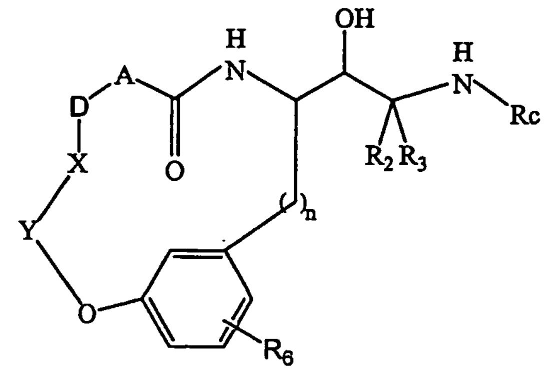
R_{aryl} is phenyl or pyridin-3-yl, each of which is optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl, trifluoromethyl, or halogen.

4. A compound according to claim 1 having the formula



(Xa)

5. A compound according to claim 1 having the formula



6. A compound according to claim 5 wherein

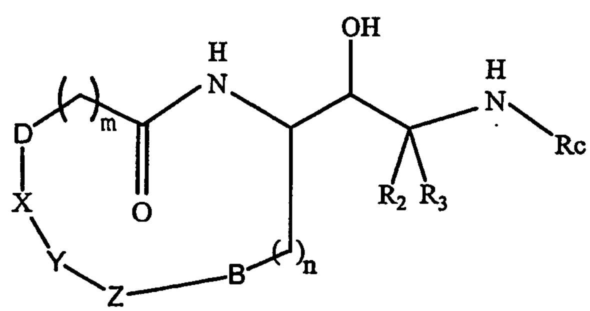
R_6 is halogen;

R_2 and R_3 are hydrogen;

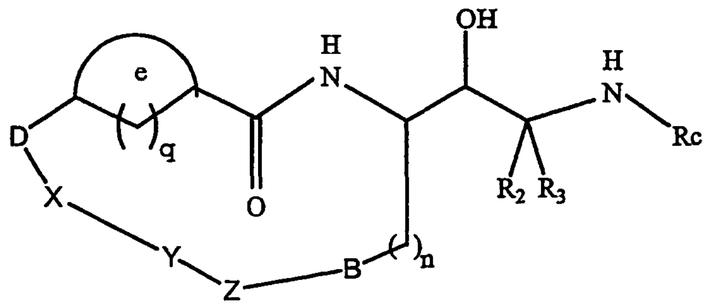
Y is C_1-C_6 alkyl; and

R_c is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl, each of which is optionally substituted with one or two R_{200}.

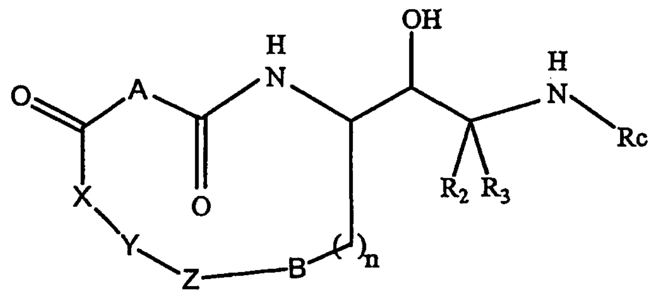
7. A compound according to claim 1 having the formula



8. A compound according to claim 1 having the formula

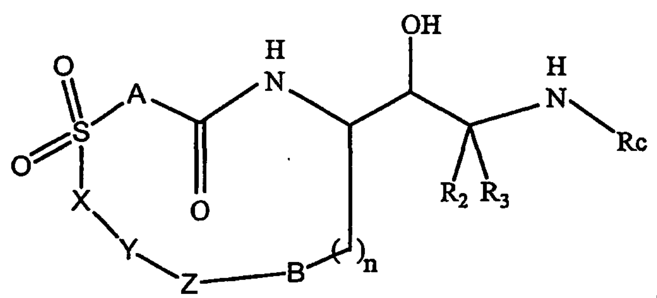


9. A compound according to claim 1 having the formula



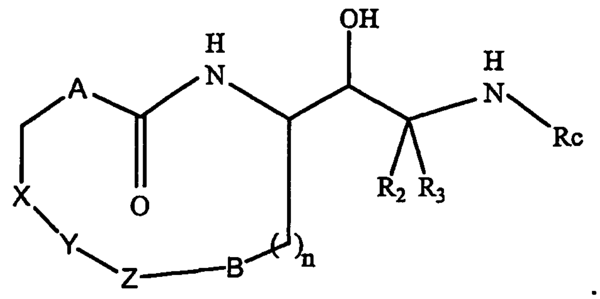
10. A compound according to claim 9 wherein X is NR_7.

11. A compound according to claim 1 having the formula

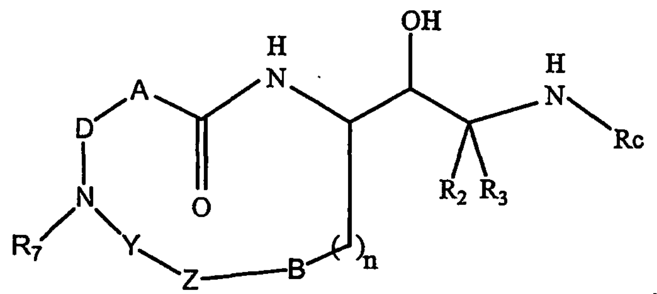


12. A compound according to claim 11 wherein X is NR_7.

13. A compound according to claim 1 having the formula

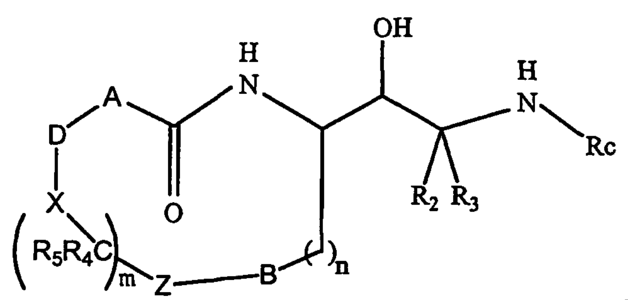


14. A compound according to claim 1 having the formula



15. A compound according to claim 14 wherein R_7 is hydrogen or C_1-C_6 alkyl.

16. A compound according to claim 1 having the formula

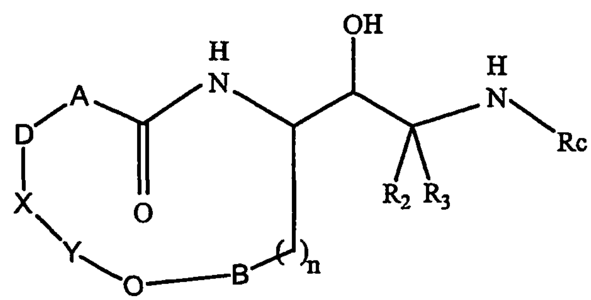


17. A compound according to claim 16 wherein m is 3-5.

18. A compound according to claim 17 wherein m is 4, and each R_4 and R_5 independently is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloC_1-C_6 alkyl, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, and C_3-C_6 cycloalkyl.

19. A compound according to claim 18 wherein each R_4 and R_5 is hydrogen, except that one R_4 or R_5 is selected from hydrogen, C_1-C_6 alkyl and C_1-C_6 alkoxyC_1-C_6 alkyl.

20. A compound according to claim 1 having the formula



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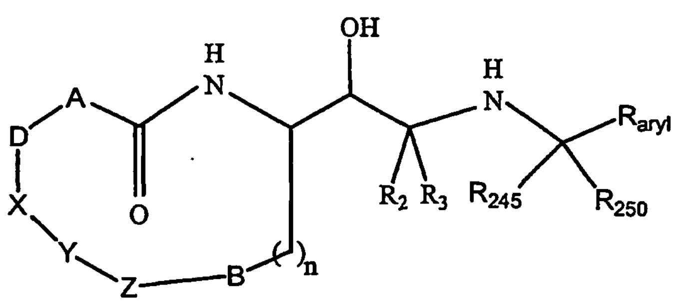
21. A compound according to claim 20 wherein X is NR_7 and Y is $-(CR_4R_5)_m-$ or C_3-C_6 alkenyl.

22. A compound according to claim 1 having the formula



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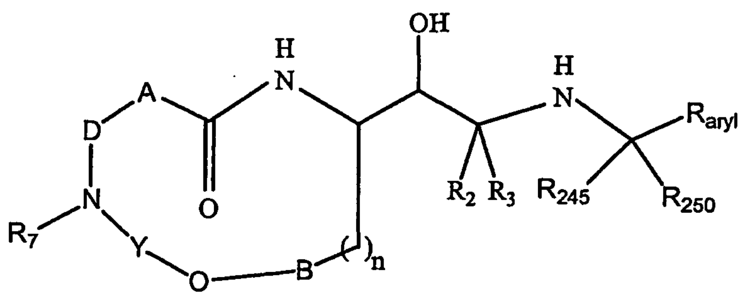
23. A compound according to claim 22 wherein
n is 1; and
R_{aryl} is phenyl or pyridin-3-yl, each of which is optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl, trifluoromethyl, or halogen.

24. A compound according to claim 23 wherein n is 1 and phenyl is optionally substituted with halogen or C_1-C_6 alkyl.

25. A compound according to claim 1 which is

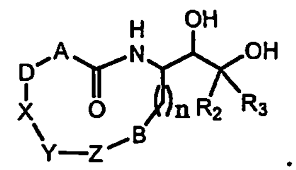


26. A compound according to claim 25 wherein n is 1-3 and
R_{aryl} is phenyl independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2$-NH-C_1-C_6 alkyl, -SO_2-N(C_1-C_6 alkyl)$_2$, -SO_2-(C_1-C_4 alkyl), -CO-NH_2, -CO-NH-C_1-C_6 alkyl, -CO-N(C_1-C_6 alkyl)$_2$,
C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,
C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen.

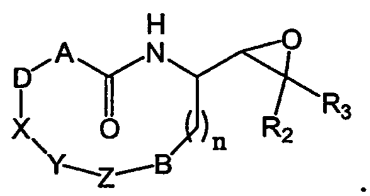
27. A compound according to claim 26 wherein n is 1 and phenyl is optionally substituted with halogen or C_1-C_6 alkyl.

28. A compound according to claim 1 having the formula



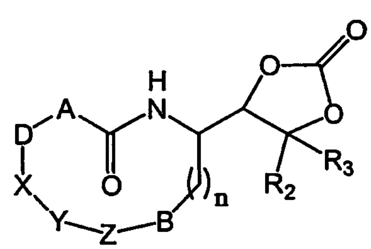
29. A compound according to claim 28 wherein R_2 and R_3 are hydrogen and X is NR_7.

30. A compound according to claim 1 having the formula



31. A compound according to claim 30 wherein R_2 and R_3 are hydrogen and X is NR_7.

32. A compound according to claim 1 having the formula



33. A compound according to claim 32 wherein R_2 and R_3 are hydrogen and X is NR_7.

34. A compound according to claim 1 which is

14-[2-(3-ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-4,7-dipropyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-4-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-4-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-11-prop-2-ynyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-11-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-11-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-11-methoxymethyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-triene-8,12-dione;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.$1^{6,10}$]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.$1^{6,10}$]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.$1^{6,10}$]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaene-2,17-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),16(20),17-trien-12-one;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-8,8-dioxo-7-propyl-2-oxa-8λ^6-thia-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-11-one;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4,7-dipropyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-7-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4-methoxymethyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

17-Fluoro-13-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

13-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-17-fluoro-4-propyl-2-oxa-7,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-8,11-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),4,16(20),17-tetraene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),4,16(20),17-tetraene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),4,16(20),17-tetraene-8,12-dione;

18-Fluoro-14-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),4,16(20),17-tetraene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-propyl-2-oxa-7,13-diaza-bicyclo[14.3.1]eicosa-1(19),4,16(20),17-tetraene-8,12-dione;

3-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

18-Fluoro-3-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-10-propyl-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

18-Fluoro-3-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

3-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-18-fluoro-7-prop-2-ynyl-15-oxa-4,10-diaza-tricyclo[14.3.1.0^{6,8}]eicosa-1(20),16,18-triene-5,9-dione;

14-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione;

14-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione;

14-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione;

14-[1-Hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione;

14-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-7-propyl-2-oxa-7,13,20-triaza-tricyclo[14.6.1.0^{17,21}]tricosa-1(22),16(23),17(21),18-tetraene-8,12-dione;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-16,20-dimethyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-methyl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.1^{6,10}]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-[2-(3-Ethyl-benzylamino)-1-hydroxy-ethyl]-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.16,10]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[1-(3-Ethyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.16,10]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

4-{2-[1-(3-Ethynyl-phenyl)-cyclopropylamino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.16,10]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one;

8-Fluoro-4-[1-hydroxy-2-(3-trifluoromethyl-benzylamino)-ethyl]-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.16,10]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one; and

4-{2-[(5-Ethyl-pyridin-3-ylmethyl)-amino]-1-hydroxy-ethyl}-8-fluoro-20-oxazol-2-yl-16-propyl-11-oxa-3,16-diaza-tricyclo[16.3.1.16,10]tricosa-1(22),6(23),7,9,18,20-hexaen-2-one.

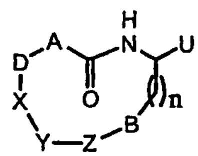
35. A compound according to claim 6 wherein
Y is n-butylene; and
R_c is phenyl or pyridin-3-yl optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkynyl or trifluoromethyl.

36. A method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI), for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy, for treating other degenerative dementias, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound of claim 1.

37. A method of treatment according to claim 1 where the therapeutically effective amount for oral administration is from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration is from about 0.5 to about 100 mg/day; for depo administration and implants is from about 0.5 mg/day to about 50 mg/day; for topical administration is from about 0.5 mg/day to about 200 mg/day; for rectal administration is from about 0.5 mg to about 500 mg.

38. Use of a compound of claim 1 for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI), for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy, for treating other degenerative dementias, diffuse Lewy body type of Alzheimer's disease.

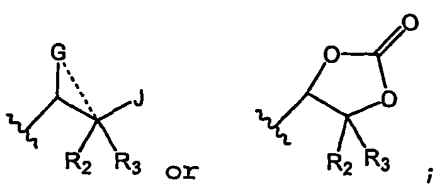
39. A method for making a compound of the formula:



(X)

and pharmaceutically acceptable salts thereof wherein

U is



--- is an optional bond;

J is $-CH_2OH$ or $-NH-R_c$ when --- is not a bond, or absent when --- is a bond;

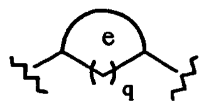
G is OH when --- is not a bond or -O- when --- is a bond;

n is 0-6;

A, B and Y are the same or different and represent

$-(CR_4R_5)_m-$; or

C_2-C_6 alkenyl optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

 , where

q is 0 or 1; and

the "e" ring is

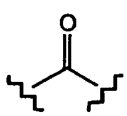
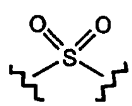
aryl or heteroaryl, each of which is optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$; or

a carbocyclic ring having three, four, five or six atoms in which one, two or three of such atoms are optionally hetero atoms independently selected from O, N, and S and where the carbocyclic ring is optionally substituted with one, two or three groups independently selected from R_6, $R_{6'}$ and $R_{6''}$;

m is 1-6;

R_4 and R_5 independently are H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, haloC_1-C_6 alkyl, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, or C_3-C_6 cycloalkyl;

D is $-CH_2-$, or

 or  ;

X is absent, O, or $-NR_7-$;

Z is absent, O, S, $-NR_7-$, -C(=O)-, -O-C(=O)-, -C(=O)-O-, -NHC(=O)-, or -C(=O)NH-;

R_7 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_1-C_6 alkoxyalkyl;

R_6, $R_{6'}$ and $R_{6''}$ independently are

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

-$(CH_2)_{0-4}$-O-(C_1-C_6 alkyl), where the alkyl portion is optionally substituted with one, two, three, four, or five groups independently selected from halogen; or

-OH, -NO_2, halogen, -CO_2H, -C≡N, -$(CH_2)_{0-4}$-CO-NR_8R_9, -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkynyl), -$(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl), -$(CH_2)_{0-4}$-R_{aryl}, -$(CH_2)_{0-4}$-$R_{heteroaryl}$, -$(CH_2)_{0-4}$-$R_{heterocyclyl}$, -$(CH_2)_{0-4}$-CO-R_{aryl}, -$(CH_2)_{0-4}$-CO-$R_{heteroaryl}$, -$(CH_2)_{0-4}$-CO-$R_{heterocyclyl}$, -$(CH_2)_{0-4}$-CO-R_{10}, -$(CH_2)_{0-4}$-CO-O-R_{11}, -$(CH_2)_{0-4}$-SO_2-NR_8R_9, -$(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl), -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl), -$(CH_2)_{0-4}$-N(H or R_{11})-CO-O-R_{11}, -$(CH_2)_{0-4}$-N(H or R_{11})-CO-N$(R_{11})_2$, -$(CH_2)_{0-4}$-N(H or R_{11})-CS-N$(R_{11})_2$, -$(CH_2)_{0-4}$-N(-H or R_{11})-CO-R_8, -$(CH_2)_{0-4}$-NR_8R_9, -$(CH_2)_{0-4}$-R_{10}, -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl), -$(CH_2)_{0-4}$-O-P(O)-$(O-R_{aryl})_2$, -$(CH_2)_{0-4}$-O-CO-N$(R_{11})_2$, -$(CH_2)_{0-4}$-O-CS-N$(R_{11})_2$, -$(CH_2)_{0-4}$-O-(R_{11}), -$(CH_2)_{0-4}$-O-(R_{11})-COOH, -$(CH_2)_{0-4}$-S-(R_{11}), C_3-C_7 cycloalkyl, -$(CH_2)_{0-4}$-N(-H or R_{11})-SO_2-R_7, or -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl;

R_8 and R_9 are the same or different and represent -H, -C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), -C_1-C_6 alkenyl, -C_1-C_6 alkynyl, or -C_1-C_6 alkyl chain with one double bond and one triple bond; or -C_1-C_6 alkyl optionally substituted with -OH or -NH_2; or;

$-C_1-C_6$ alkyl optionally substituted with one, two or three groups independently selected from halogen; or

heterocyclyl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6\ alkyl)_2$, $-SO_2-(C_1-C_4\ alkyl)$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, oxo, $-CO-N(C_1-C_6\ alkyl)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen; or

aryl or heteroaryl, each of which is optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6\ alkyl)_2$, $-SO_2-(C_1-C_4\ alkyl)$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, and $-CO-N(C_1-C_6\ alkyl)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl,

halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three of halogen;

R_{10} is heterocyclyl optionally substituted with one, two, three or four groups independently selected from C_1-C_6 alkyl;

R_{11} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-R_{aryl}$, or $-(CH_2)_{0-2}-R_{heteroaryl}$;

R_{aryl} is aryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heteroaryl}$ is heteroaryl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl$)_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, or $-CO-N(C_1-C_6$ alkyl$)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

$R_{heterocyclyl}$ is heterocyclyl optionally substituted with one, two or three groups independently selected from halogen, amino, mono- or dialkylamino, -OH, -C≡N, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6\ alkyl)_2$, $-SO_2-(C_1-C_4\ alkyl)$, $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, =O, $-CO-N(C_1-C_6\ alkyl)_2$,

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino,

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, and

C_1-C_6 alkoxy optionally substituted with one, two or three groups independently selected from halogen;

R_2 is

-H; or $-(CH_2)_{0-4}-R_{aryl}$ and $-(CH_2)_{0-4}-R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

C_2-C_6 alkenyl, C_2-C_6 alkynyl or $-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl, each of which is optionally substituted with one, two or three groups independently selected from C_1-C_3

alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino;

R_3 is -H, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_{0-4}-R_{aryl}$, or $-(CH_2)_{0-4}-R_{heteroaryl}$; or

C_1-C_6 alkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

$-(CH_2)_{0-4}$- C_3-C_7 cycloalkyl optionally substituted with one, two or three groups independently selected from C_1-C_3 alkyl, halogen, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a carbocycle of three, four, five, six, or seven carbon atoms, where one atom is optionally a heteroatom selected from the group consisting of -O-, -S-, $-SO_2-$, and $-NR_8-$;

R_C is hydrogen, $-(CR_{245}R_{250})_{0-4}$-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-aryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-aryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-aryl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heteroaryl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-heterocyclyl, $-(CR_{245}R_{250})_{0-4}$-heterocyclyl-aryl, $-[C(R_{255})(R_{260})]_{1-3}-CO-N-(R_{255})_2$, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, -CH(heterocyclyl)$_2$, -CH(aryl)(heteroaryl), $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH)-(CH_2)_{0-1}$-aryl, $-(CH_2)_{0-1}-CH((CH_2)_{0-6}-OH-(CH_2)_{0-1}$-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C_1-C_4 alkyl), $-CH(-CH_2-OH)-CH(OH)-phenyl-NO_2$, ($C_1$-$C_6$ alkyl)-O-(C_1-C_6 alkyl)-OH; $-CH_2-NH-CH_2-CH(-O-CH_2-CH_3)_2$, $-(CH_2)_{0-6}-C(=NR_{235})(NR_{235}R_{240})$, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of

R_{205}, $-OC{=}ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), -SH, $-NR_{235}C{=}ONR_{235}R_{240}$, $-C{=}ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or

$-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205}, $-CO_2H$, and $-CO_2-(C_1-C_4$ alkyl), or

cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocyclyl wherein one, two or three carbons of the cyclopentyl, cyclohexyl, or cycloheptyl is optionally replaced with a heteroatom independently selected from NH, NR_{215}, O, or $S(=O)_{0-2}$, and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group can be optionally substituted with one or two groups that are independently R_{205}, =O, $-CO-NR_{235}R_{240}$, or $-SO_2-(C_1-C_4$ alkyl), or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R_{200}, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{200} at each occurrence is independently selected from -OH, $-NO_2$, halogen, $-CO_2H$, C≡N, $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}$-CO-aryl, $-(CH_2)_{0-4}$-CO-heteroaryl, $-(CH_2)_{0-4}$-CO-heterocyclyl, $-(CH_2)_{0-4}-CO-O-R_{215}$, $-(CH_2)_{0-4}-SO_2-NR_{220}R_{225}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-O-R_{215}$, $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-N-CS-N(R_{215})_2$, $-(CH_2)_{0-4}-N(-H$ or $R_{215})-CO-R_{220}$, $-(CH_2)_{0-4}-NR_{220}R_{225}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(OR_{240})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{215})_2$, $-(CH_2)_{0-4}-O-(R_{215})$, $-(CH_2)_{0-4}-O-(R_{215})$-COOH, $-(CH_2)_{0-4}-S-(R_{215})$, $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with 1, 2, 3,

or 5 -F), C_3-C_7 cycloalkyl, -$(CH_2)_{0-4}$-N(H or R_{215})-SO_2-R_{220}, -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 R_{205} groups, or

C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1 or 2 R_{205} groups, wherein

the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210};

R_{205} at each occurrence is independently selected from C_1-C_6 alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, NH_2, NH(C_1-C_6 alkyl) or N-(C_1-C_6 alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -$NR_{220}R_{225}$, OH, C≡N, -CO-(C_1-C_4 alkyl), -SO_2-$NR_{235}R_{240}$, -CO-$NR_{235}R_{240}$, -SO_2-(C_1-C_4 alkyl), =O, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups;

R_{215} at each occurrence is independently selected from C_1-C_6 alkyl, -$(CH_2)_{0-2}$-(aryl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and -$(CH_2)_{0-2}$-(heteroaryl), -$(CH_2)_{0-2}$-(heterocyclyl), wherein

the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{210};

R_{220} and R_{225} at each occurrence are independently selected from -H, $-C_3-C_7$ cycloalkyl, $-(C_1-C_2$ alkyl$)-(C_3-C_7$ cycloalkyl$)$, $-(C_1-C_6$ alkyl$)-O-(C_1-C_3$ alkyl$)$, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_1-C_6$ alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, or

$-C_1-C_{10}$ alkyl optionally substituted with -OH, $-NH_2$ or halogen, wherein

the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R_{270} groups

R_{235} and R_{240} at each occurrence are independently H, or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently selected from -H, C_1-C_4 alkyl, C_1-C_4 alkylaryl, C_1-C_4 alkylheteroaryl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and phenyl; or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, $-SO_2-$, and $-NR_{220}-$;

R_{255} and R_{260} at each occurrence are independently selected from -H, $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6$ alkyl$)$, $-(C_1-C_4$ alkyl$)$-aryl, $-(C_1-C_4$ alkyl$)$-heteroaryl, $-(C_1-C_4$ alkyl$)$-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$-aryl, $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$-heteroaryl, $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$-heterocyclyl, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups, wherein

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R_{205}, R_{210}, or

C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210}, and wherein

each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{265} at each occurrence is independently -O-, -S- or -N(C_1-C_6 alkyl)-; and

R_{270} at each occurrence is independently R_{205}, halogen C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $NR_{235}R_{240}$, -OH, -C≡N, -CO-(C_1-C_4 alkyl), -SO_2-$NR_{235}R_{240}$, -CO-$NR_{235}R_{240}$, -SO_2-(C_1-C_4 alkyl), =O, or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/18719

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/395 C07D273/02 C07D291/08 C07D413/04 C07D413/12
A61P25/28 C07D413/14 C07D419/12 C07D498/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FAIRLIE D P ET AL: "CONFORMATIONAL SELECTION OF INHIBITORS AND SUBSTRATES BY PROTEOLYTIC ENZYMES: IMPLICATIONS FOR DRUG DESIGN AND POLYPEPTIDE PROCESSING" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 7, no. 43, 2000, pages 1271-1281, XP002950831 ISSN: 0022-2623 compounds 1 and 3 abstract	1-39
A	WO 96 16950 A (FAIRLIE DAVID ;REID ROBERT (AU); ABBENANTE JOHN (AU); BERGMAN DOUG) 6 June 1996 (1996-06-06) claims 1,2	1-39

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2002	10/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

INTERNATIONAL SEARCH REPORT	tional application No. ?CT/US 02/18719

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 36 and 37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/18719

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9616950 A	06-06-1996	AU 4111896 A	19-06-1996
		WO 9616950 A1	06-06-1996
		US 6043357 A	28-03-2000